FLOXIN® Otic

(ofloxacin otic) solution 0.3%

Product Dossier

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I. Executive Summary

Otic diseases account for millions of visits to otolaryngologists, pediatricians and family physicians in the United States annually. Topical otic antibiotics as well as systemic antibiotics are frequently prescribed for these conditions, although some antimicrobial agents are associated with a risk for ototoxicity or lack of adequate microbial coverage.[1-3] Otitis externa (OE), chronic suppurative otitis media (CSOM) with a perforated tympanic membrane, and acute otitis media with tympanostomy tubes (AOM TT) are three conditions for which ototopical medications can constitute first-line treatment.[1] The following information concerns these common otic infections and considerations for treatment.

Background

- Otitis externa (swimmer's ear) is typically a localized bacterial process of the external auditory canal that generally responds to treatment with topical antimicrobial agents.
- Acute otitis media with tympanostomy tubes and CSOM both involve a non-intact tympanic membrane. In addition to the usual pathogens seen in acute otitis media with an intact tympanic membrane *Pseudomonas aeruginosa* and *Staphylococcus aureus* are typical causative pathogens for both of these ear conditions.[1]
- These infections can be successfully treated with an appropriate ototopical agent, which should cover *Pseudomonas aeruginosa* and *Staphylococcus aureus* in addition to the usual pathogens seen in acute otitis media.[1]
- No oral agent currently approved by the FDA for pediatric use is effective against *Pseudomonas aeruginosa.*
- Some ototopical agents, such as aminoglycosides, that provide coverage for *Pseudomonas aeruginosa* are associated with a risk for ototoxicity when used with a non-intact tympanic membrane.

FLOXIN® Otic (ofloxacin otic) solution 0.3%, a topical fluoroquinolone, provides excellent coverage for *Pseudomonas aeruginosa* in AOM TT, CSOM with perforated tympanic membranes, and OE. Distinct from other ototopical medications, FLOXIN Otic is indicated for all three infections:

- Otitis Externa in adults and pediatric patients, 6 months and older, due to *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*
- Chronic Suppurative Otitis Media in patients 12 years and older with perforate tympanic membranes due to *Proteus mirabilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus*
- Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae*

Benefits of FLOXIN® Otic

- Coverage for the major pathogens, including *Pseudomonas aeruginosa*, in three common ear infections.
- FLOXIN Otic is approved as first-line monotherapy.
- Topical administration at the site of infection can obviate the need for systemic antibiotic therapy in the absence of systemic symptoms or serious underlying disease.
- No evidence of ototoxicity, in contrast to topical aminoglycoside preparations. This statement is based on pre-clinical animal data and 30 pediatric subjects with AOM TT who were treated with FLOXIN Otic and tested for audiometric parameters.[4] No change in hearing function occurred in these subjects.
- Steroid-free, causing no concerns about potential systemic absorption of potent corticosteroids.
- Only ototopical antibiotic that is approved for once-daily dosing in OE.
- First approved agent for use in the middle ear with a non-intact membrane.
- Only FDA approved therapy in CSOM due to *Staphylococcus aureus, Proteus mirabilis, and Pseudomonas aeruginosa* in patients 12 years and older with perforated tympanic membranes.
- Daiichi Sankyo, Inc.. is dedicated to promoting the message of appropriate antibiotic use in OE, AOM TT, and CSOM.

Efficacy

- FLOXIN Otic administered once daily is as effective as Cortisporin Otic Suspension administered four times daily for the treatment of OE (7 to 10 days).[5,6]
- FLOXIN Otic is the first and only approved therapy for chronic suppurative otitis media with a perforated tympanic membrane. In clinical trials, the clinical cure rates in subjects with CSOM in whom pathogens were identified, were as follows: *Pseudomonas aeruginosa* 97%, *Staphylococcus aureus* 90%, *Proteus mirabilis* 100%.[7]
- FLOXIN Otic has been proven to be as effective as Augmentin for inducing resolution of otorrhea in subjects who had AOM TT, [76% versus 69%, respectively (95%CI -3.7 to 18.2%)].4 Since Augmentin is not effective against *Pseudomonas aeruginosa*, subjects with *Pseudomonas aeruginosa* as the sole pre-therapy pathogen were removed from the study and replaced with another subject.
- Very high concentrations of antibiotic achievable with ototopical preparations have generally been considered sufficient to explain high eradication rates of infecting organisms. This is thought to be one reason for the low incidence of treatment emergent bacterial resistance with direct, ototopical administration.[8]

Safety

- FLOXIN® Otic is safe and generally well-tolerated.[2,4-6,7,9]
- FLOXIN Otic has a much lower incidence of diarrhea (< 1%) compared to Augmentin (27%) in children with AOM TT.[4]
- The most commonly reported adverse event with once-daily FLOXIN Otic administration in clinical trials of subjects with otitis externa (n=310) was application site reaction (16.8%).[* 5] In an open label trial (n=489), the application site reaction was (0.6%).6 (See Section II A for additional adverse events.)
- The most commonly reported adverse event in clinical trials of subjects with AOM TT and CSOM (n=656) was taste perversion (7%).10 (See Section II A for additional adverse events.)
- FLOXIN Otic is demonstrated to be safe to use on both sides of the tympanic membrane. Clinical trial results showed no evidence of hearing loss based on a study with 30 pediatric subjects with AOM TT.[4]
- FLOXIN Otic is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication and should be discontinued at the first sign of allergic reaction.[10] (See full prescribing information for a complete list of all contraindications.)

FLOXIN Otic Indications and Dosing[10]

Otic Infection	Pathogens	Patient age	Dosage of FLOXIN Otic	Therapy Length
Otitis externa	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Escherichia coli*	6 months to 13 years	5 drops (0.25 mL) instilled into the affected ear once daily	7 days
		≥ 13 years	10 drops (0.5 mL) instilled into the affected ear once daily	7 days
Acute otitis media with tympanostomy tubes	*Staphylococcus aureus* *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Pseudomonas aeruginosa*	1 to 12 years	5 drops (0.25 mL) instilled into the affected ear twice daily	10 days
Chronic suppurativeotitis media with perforated tympanic membranes	*Staphylococcus aureus* *Proteus mirabilis* *Pseudomonas aeruginosa*	≥ 12 years	10 drops (0.5 mL) instilled into the affected ear twice daily	14 days

* An unexpected increased incidence of application site reaction was seen in 2 studies and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This observation is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions. (See prescribing information for full safety information.)

II. Product Information

A. Product description

1. Generic name, brand name, therapeutic class, dosage forms

Generic name:	ofloxacin otic solution 0.3%
Brand name:	FLOXIN® Otic
Therapeutic class:	quinolone topical antibiotic
Dosage forms:	otic drops
Availability:	plastic dropper bottles containing 5 mL and 10 mL single-dispensing container (SDC) delivers 0.25 mL of medication; SDCs are packaged two per foil pouch (see Appendix)

2. Food and Drug Administration (FDA) approved indications

FLOXIN Otic (ofloxacin otic) solution 0.3% is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

- **Otitis Externa** due to *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli* in patients 6 months and older
- **Chronic Suppurative Otitis Media** due to *Staphylococcus aureus, Proteus mirabilis, and Pseudomonas aeruginosa* in patients 12 years and older with perforated tympanic membranes
- **Acute Otitis Media** due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Pseudomonas aeruginosa* in pediatric patients 1 year and older with tympanostomy tubes

3. FDA Approval Date: December 16, 1997

4. Pharmacology/Microbiology

Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme that controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms, including those most widely accepted to be the primary causative agents in the medical conditions for which FLOXIN Otic is indicated:

aerobes, Gram-positive:	**aerobes, Gram-negative:**
Staphylococcus aureus	*Escherichia coli*
Streptococcus pneumoniae	*Haemophilus influenzae*
	Moraxella catarrhalis
	Proteus mirabilis
	Pseudomonas aeruginos

5. Pharmacokinetics

Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two singledose studies, mean ofloxacin serum concentrations were low in adult subjects with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1 ng/mL (n=3) and 5.4 ng/mL (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level of ofloxacin detected was 10 ng/mL after administration of a 0.3% solution. Ofloxacin was detectable in the middle ear mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2 to 602 μg/g after otic administration of a 0.3% solution. Ofloxacin was present in high concentrations in otorrhea (389 - 2850 μg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with CSOM and perforated tympanic membranes.10 However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

6. Contraindications

FLOXIN® Otic is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

7. Warnings/Precautions

Not for ophthalmic use
Not for injection

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

General precautions: As with other anti-infective preparations, prolonged use may result in over-growth of nonsusceptible organisms, including fungi. If the infection is not improved after one week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guin systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of ea pig following otic administration of 0.3% ofloxacin for one month

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

8. Information for patients

Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

9. Special populations

a. Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted. Ofloxacin was not mutagenic in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micro-nucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with FLOXIN® Otic twice per day.

b. Pregnancy, teratogenic effects: Pregnancy category C

Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

c. Nonteratogenic effects: Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and wellcontrolled
studies in pregnant women. Ofloxacin otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

d. Nursing mothers

In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

e. Pediatric use

Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- Six months and older: otitis externa with intact tympanic membranes
- One year and older: acute otitis media with tympanostomy tubes
- Twelve years and older: chronic suppurative otitis media with perforated tympanic membranes

Safety and efficacy in pediatric patients below these ages have not been established. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product. No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters. Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

f. Geriatric use

No studies have been designed to look specifically at this population. However, sixteen geriatric subjects (3.6%) were enrolled in 1 (PRT 020) of the 3 pivotal trials for obtaining once-daily dosage in otitis externa (OE) for 7 days.6 Twelve subjects out of 16 (75%) > 65 years old were cured. Of these 12 subjects, 5 were microbiologically evaluable and all 5 had eradication.

10. Adverse effects

Phase III registration trials, which examined the safety and effectiveness of twice-daily administration schedules, included 229 subjects with OE who were treated twice daily with ofloxacin otic solution (Studies 002/003).9 In phase III clinical trials performed in support of once-daily dosing, 799 subjects with OE and intact membranes were treated with ofloxacin otic solution. The studies that served as the basis for once-daily approval were 0206 (pediatrics, adolescents and adults), 0165 (adolescents and adults), and 0175 (pediatrics). The reported treatment-related adverse events are listed in Table 1 for both once- and twice-daily administration.

Table 1. Adverse events in subjects with otitis externa[5,6,9]

Adverse Event	Incidence Rate		
	Studies 002/003† Twice daily (N= 229)	**Studies 016/017† Once daily (N=310)**	**Study 020† Once daily (N=489)**
Application Site Reaction	3%	16.8%	0.6%
Pruritus	4%	1.2 %	1.0 %
Earache	1%	0.6 %	0.8 %
Dizziness	1%	0.0 %	0.6 %
Headache	0%	0.3 %	0.2 %
Vertigo	1%	0.0 %	0.0 %

† Studies 002/003 (twice daily) and 016/017 (once daily) were active-controlled and comparative. Study 020 (once daily) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfatehydrocortisone).[5] This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once-daily dosing studies in subjects with OE, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension, and fungal infection.[5,6]

In twice-daily dosing studies that were done in subjects who had OE the following treatmentrelated adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.[10]

In phase III registration trials, 656 subjects with either acute otitis media with tympanostomy tubes (AOM TT) or chronic suppurative otitis media (CSOM) with perforated tympanic membranes were treated with ofloxacin otic solution twice daily.[4,7] The following treatmentrelated adverse events occurred in 1% or more of the subjects with non-intact tympanic membranes (Table 2).

Table 2. Adverse events in subjects with acute otitis media with tympanostomy tubes or chronic suppurative otitis media with perforated tympanic membranes[10]

Adverse Event	Frequency (n = 656)
Taste Perversion	7%
Earache	1%
Pruritus	1%
Paraesthesia	1%
Rash	1%
Dizziness	1%

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), and fever (0.3%).[10] The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.[10]

11. Post-marketing adverse events

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

12. Availability, dosing and administration

a. Availability

FLOXIN® Otic is supplied in 5 and 10 mL plastic dropper bottles and as single-dispensing containers (SDCs). The SDC delivers 0.25 mL of medication; SDCs are packaged two per foil pouch (see Appendix).

	NDC codes
5 mL bottle	63395-101-05
10 mL bottle	63395-101-10
SDC	63395-101-11

b. Dosing

Table 3. FLOXIN Otic indications and dosing*

Indication**	Patient age	Dosage	Length of therapy
Otitis externa	6 months and older	5 drops (0.25 mL) instilled into the affected ear once daily	7 days
	= 13 years	10 drops (0.5 mL) instilled into the affected ear once daily	7 days
Acute otitis media with tympanostomy tubes	1 to 12 years	5 drops (0.25 mL) instilled into the affected ear twice daily	10 days
Chronic suppurative otitis media with perforated tympanic membranes	= 12 years	10 drops (0.5 mL) instilled into the affected ear twice daily	14 days

* For dosing information on use of single-dispensing containers (SDCs), see Appendix

** For a list of covered pathogens see full prescribing information

c. Administration

Otitis externa:

The solution should be warmed by holding the container in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the medication into the ear canal. Repeat, if necessary, for the opposite ear.

Acute otitis media in patients with tympanostomy tubes and
Chronic suppurative otitis media with perforated tympanic membranes:

The solution should be warmed by holding the container in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. The tragus should be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

13. Use with concomitant therapies

We are not aware of studies undertaken on the use of ofloxacin otic with other therapies.

B. Comparison with other agents in the therapeutic area

1. Oral antibiotics

The role of oral antimicrobial treatment of acute middle-ear infection post tympanostomy tube placement is a subject of active investigation.[11] This is due in large part to the unique mix of pathogens found in aural discharge from children (6 months to 6 years) with otorrhea post tube placement, which include the following pathogens occurring either uniquely or in combination: *Staphylococcus aureus*, *Streptococcus pneumoniae* (both penicillin-sensitive and penicillin-nonsusceptible), non-typeable *Haemophilus influenzae* (both beta-lactamase positive and negative) and *Pseudomonas aeruginosa*.[12] At present, oral antibiotics that are both effective against *Pseudomonas* and safe to use in children are not available.

The use of oral antibiotics (such as Augmentin) has been shown to be effective in treating AOM TT but only when *Pseudomonas aeruginosa* is not part of the spectrum of potential causative pathogens. Therefore, the use of oral antibiotics in treating middle ear infections when the tympanic membrane is not intact is not recommended. Oral antibiotic use also needs to be balanced against its systemic adverse reactions, notably diarrhea, and the concern that inappropriate use of systemic antibiotics contributes to bacterial resistance.

2. Other topical preparations

Cortisporin® Otic Solution and Suspension (both containing neomycin, polymyxin B sulfate, and hydrocortisone), are ototopical medications indicated for use in OE.[13,14] The aminoglycoside (neomycin) component of the Cortisporin Otic preparations contributes to the risk of both ototoxic and local side effects.

Neomycin can induce permanent sensorineural hearing loss due to cochlear damage. The risk of ototoxicity is greater with prolonged use. Therefore, duration of therapy should be limited to 10 consecutive days. Neomycin may also cause cutaneous sensitization, causing symptoms such as itching and erythema. Cortisporin Otic Solution should not be used in any patient with a perforated tympanic membrane. Lastly, Cortisporin Otic Solution contains potassium metabisulfite that may cause allergic-type reactions, including anaphylaxis.[13] Sulfite sensitivity is seen more frequently in patients who have asthma.

In contrast, there is no evidence of ototoxicity with the use of FLOXIN® Otic in AOM TT based on pre-clinical animal data and 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.[4] No change in hearing function occurred in these subjects. FLOXIN Otic is a safe option for use in AOM TT, CSOM with a perforated tympanic membrane, and OE when the integrity of the tympanic membrane is in doubt. FLOXIN Otic has a near neutral pH and is steroid-free.

Cipro® HC Otic Suspension (ciprofloxacin 0.2%, hydrocortisone 1%) and Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) are combination products containing corticosteroids.[15,16] The use of a potent corticosteroid such as dexamethasone in the middle ear space may potentially raise safety concerns regarding hypothalamic pituitary axis (HPA) suppression, especially if the product is used for prolonged periods. According to the prescribing information sheet for Ciprodex, even after a single, bilateral 4-drop dose of Ciprodex (0.28 mg of dexamethasone), the peak plasma concentrations of dexamethasone were observed to be between 13.5 ng/dl to 510 ng/dl.[15] Since it has been shown that a plasma dexamethasone level of greater than 200 ng/dl is sufficient to cause HPA suppression,[17] safety issues may arise.

Furthermore, dexamethasone has a long biologic half-life of 36-54 hours18 (much longer than its reported plasma half-life of 5 hours), thus increasing the potential for concern with each successive dose. The administration of a single, bilateral 4-drop dose may deliver up to 0.28 mg of dexamethasone to the middle ear. If a 7-day course of twice-daily therapy is completed, a total of 3.92 mg of dexamethasone would be administered to a pediatric patient with bilateral ear infections, seen in approximately 20% of cases.

Table 4. Comparison of ototopical agents[1,10,13-16,18]

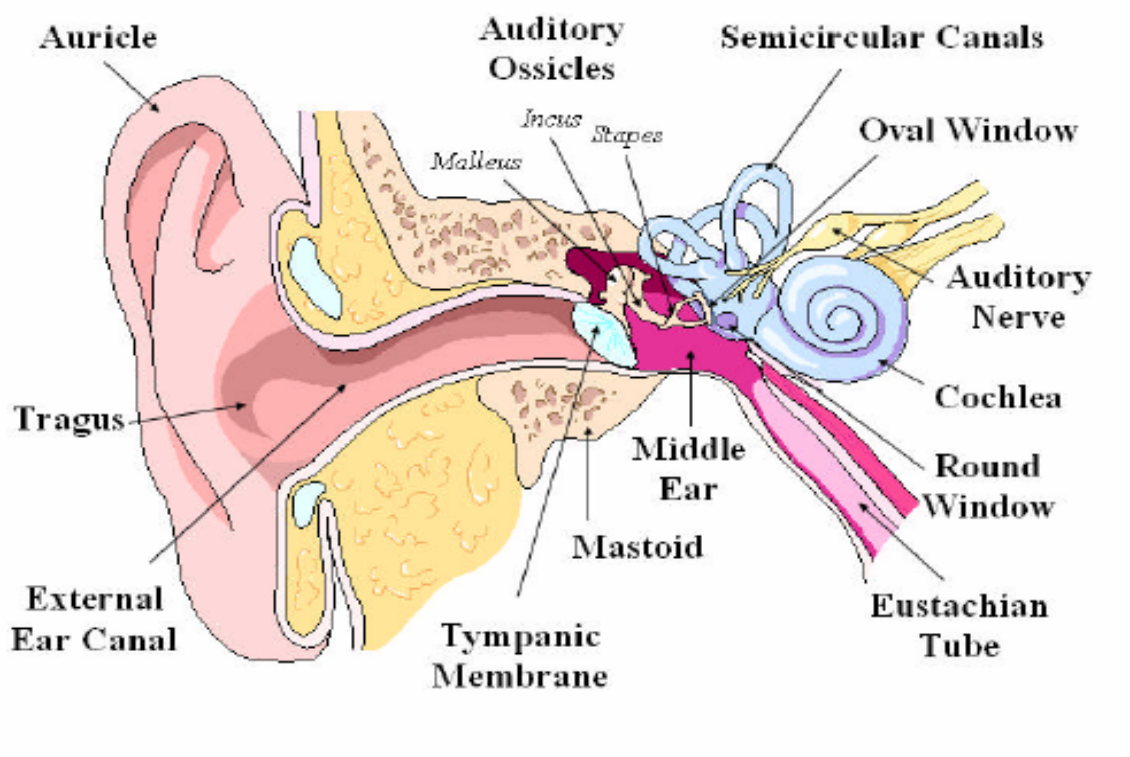
	FLOXIN® Otic Solution	**Cortisporin Otic Solution/Suspension**	**Cipro HC Otic Suspension**	**Ciprodex Suspension**
Components	ofloxacin otic solution 0.3%	neomycin polymyxin B sulfate hydrocortisone 1%	ciprofloxacin HCL 0.2% hydrocortisone 1%	ciprofloxacin 0.3% dexamethasone 0.1%
Indications and pathogens covered	**<u>Otitis externa:</u> in patients > 6 months due to:** *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus* **<u>Chronic suppurative otitis media</u> in patients > 12 due to** *Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus* **<u>Acute otitis media</u> in pediatric patients > 1 with tympanostomy tubes due to** *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae*	**<u>Otitis externa</u> due to** *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Klebsiella-Enterobacter species, Neisseria species*	**<u>Otitis externa</u> in patients > 1 due to** *Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis*	**<u>Otitis externa</u> in patients > 6 months due to** *Staphylococcus aureus, Pseudomonas aeruginosa* **<u>Acute otitis media</u> in pediatric patients > 6 months with tympanostomy tubes due to** *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae*
Frequency of dosing				
OE	Once daily for 7 days	Three to four times daily for 10 days	Two times daily for 7 days	Two times daily for 7 days
AOM TT	Two times daily for 10 days	Contraindicated	Contraindicated	Two times daily for 7 days
CSOM	Two times daily for 14 days	Contraindicated	Contraindicated	Not indicated

III. Place in Therapy

Three common conditions for which ototopical medications constitute first-line treatment are otitis externa (OE), chronic suppurative otitis media (CSOM) and acute otitis media with tympanostomy tubes (AOM TT).[1] Coverage for *Pseudomonas aeruginosa* is critical in the treatment of all 3 of these ear diseases because it is a key causative pathogen. Although systemic agents may be used for AOM TT, there are no systemic agents approved for children that have coverage for *Pseudomonas aeruginosa*. In contrast, FLOXIN® Otic, a steroid-free quinolone antibiotic in sterile solution, does provide coverage against *Pseudomonas aeruginosa*, which is an especially important consideration for treating a patient with a non-intact tympanic membrane.

In patients with a non-intact membrane, organisms that colonize the external auditory canal, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, are often isolated from middle ear drainage in addition to those commonly seen in acute otitis media.[2,19] *Pseudomonas aeruginosa* coverage is also an important consideration when treating OE, as this organism is one of the most commonly isolated pathogens.[9]

Figure 1.*



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When treating an infection of the external ear with an intact membrane, a minimal risk is incurred in exposing the external ear canal to a given agent. However, when the middle ear space is open (a condition that is seen with a chronic perforation of the tympanic membrane or the placement of a tympanostomy tube), exposure of the middle ear to ototopical agents necessitates many considerations, e.g., a caution regarding potential for ototoxicity, appropriateness of antimicrobial spectrum, and sterility. Aminoglycosides, for example, are associated with a risk of ototoxicity.[20] There is no evidence of ototoxicity with the use of FLOXIN® Otic, based on use of FLOXIN Otic in 30 pediatric subjects with AOM TT who were tested for audiometric parameters.[4] No change in hearing function occurred in these subjects. Agents introduced into the middle ear space must be sterile. FLOXIN Otic is a sterile quinolone solution with a near neutral pH.

The following sections introduce each of the diseases for which the quinolone antibacterial agent FLOXIN Otic has indications. Until FLOXIN Otic became available, there had not been any approved therapies for use in middle ear infections in children with non-intact tympanic membranes, a condition in which *Pseudomonas aeruginosa* is a frequent causative pathogen.

A. Otitis externa

1. Introduction/Definitions

Otitis externa, often called swimmer's ear, is a bacterial or fungal infection of the epithelium of the external auditory canal.[1] The external auditory canal is an epithelial-lined tube with the outer third cartilaginous and the inner two-thirds bony. The epithelium over the bony portion of the canal is thin which causes the area to be sensitive to palpation and susceptible to trauma. Otitis externa is typically a localized process that generally responds to topical antimicrobial therapy.[21]

"An episode of OE generally results from the impact of an endogenous condition of the external canal such as trauma, maceration of the skin from water exposure, or an abnormality such as an osteoma, cerumen, or a foreign body."[22] It is often associated with swimming and other water sports.[9,23] Otitis externa will affect only one ear 80 percent of the time and both ears 20 percent of the time.[22]

2. Microbiology

The most common bacterial pathogen associated with OE is *Pseudomonas aeruginosa*.[1]

3. Epidemiology and relevant risk factors

The otitis externa condition most often results from a bacterial etiology. The unique structure of the external auditory canal contributes to the development of OE.[21] The external auditory canal is warm, dark and prone to becoming moist, making it an excellent environment for bacterial and fungal growth. The most common precipitant of infection is excessive moisture, which elevates the pH and removes the protective cerumen.[21]

Cerumen creates an acidic coat containing lysozymes and other substances that probably inhibit bacterial and fungal growth. The lipid-rich cerumen is also hydrophobic and prevents water from penetrating to the skin and causing maceration.[21] Once the cerumen is removed, keratin debris absorbs water, creating a nourishing medium for bacterial growth.

Damage to the skin of the ear canal by the introduction of irritants or by cleaning or scratching, can also lead to OE. Patients with compromised skin in the ear canal, such as those who have

allergies, psoriasis, eczema, or scalp dermatitis, are especially likely to develop this infection. Common precipitants of OE are listed in Table 5.

If it is not optimally treated, especially in immunocompromised patients, the infection can spread to the surrounding tissues.[21] Otitis externa can become a life-threatening condition in the adult who also has diabetes, in which case it often is associated with vasculitis, infections, and necrosis of skull base tissues.[22]

Table 5. Common precipitants of otitis externa[21]

- Moisture (swimming, perspiration, high humidity)
- Water contaminated with bacteria
- Chronic dermatologic disease
- Trauma to the external auditory canal
- Insertion of foreign objects
- Mechanical removal of cerumen
- High environmental temperatures

4. *Clinical presentation*

Otitis externa is a common inflammatory process affecting the external auditory canal. The two common presenting symptoms of OE are earache (otalgia) and discharge from the external auditory canal (otorrhea). The signs and symptoms of OE with a bacterial etiology tend to be more intense than in other forms of the disease.[21] Due to inflammation and edema of the ear canal skin, OE can be quite painful.[1]

The extreme tenderness of the auricle and canal, and obstruction of the canal by edema and debris may make it difficult to adequately assess the integrity of the tympanic membrane in subjects with OE.[9]

5. *Approaches to treatment*

The objectives of treatment for OE are to relieve signs and symptoms of infection and promote the return of the external auditory canal to its healthy state.[9] Otitis externa is usually treated empirically without benefit of cultures.[9] Thus, a treatment selected for this condition should be one that is effective against the usual pathogens.

Meticulous and repeated cleaning of the canal to remove the otorrhea and other debris that occludes the ear canal is the cornerstone of effective treatment.[1] Occlusion keeps the canal moist, makes it difficult to visualize the tympanic membrane, and interferes with topical treatment.[21] In most cases of uncomplicated OE, topical antibiotics alone constitute first line therapy.[1] In some cases the tympanic membrane will be impossible to visualize. When the patency of the tympanic membrane is unknown because the canal is obstructed by edema and debris, an unknown perforation may expose the middle ear to potentially harmful agents. A medication specifically indicated and approved for use in middle ear infections, such as FLOXIN® Otic, is desirable.

"Oral antibiotics are rarely needed but should be used when OE is persistent, when associated otitis media may be present, or when local or systemic spread has occurred."[21] Oral antibiotics

may also be necessary when the patient has early signs of necrotizing OE or in immunocompromised patients.[21]

B. Chronic suppurative otitis media

1. *Introduction/Definitions*

Chronic suppurative otitis media (CSOM) can be defined as chronic infection of the middle earcleft with or without the presence of otorrhea through a non-intact tympanic membrane that has been unresponsive to medical management.[20,24,25] There is no consensus on the duration of chronic otorrhea.[20,25] However, two weeks to six weeks of drainage through a non-intact membrane is typically seen with chronic disease of the middle ear.[20,24]

Chronic suppurative otitis media begins with an acute onset of otitis media, either acute otitis media or otitis media with effusion.[20] A perforation may occur as a complication or sequela of otitis media. Chronic perforation of the tympanic membrane may develop after an acute perforation fails to heal or following resolution of CSOM, or during the course of chronic otitis media with effusion.[20] Chronic suppurative otitis media typically develops only after the patient has sustained many episodes of acute otitis media over a period of at least several years.

2. *Microbiology*

By definition, CSOM involves a perforated tympanic membrane; therefore, pathogens may enter the middle ear either from the external auditory canal or as a result of the loss of the middle ear air cushion by Eustachian tube reflux from the nasopharynx.[24] If there is a chronic perforation, reinfection may occur by Eustachian tube reflux of nasopharyngeal secretions containing the bacteria seen in acute otitis media (*Streptococcus pneumoniae* and *Haemophilus influenzae*).[24] Organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* may enter the middle ear directly from the external ear canal.[20]

3. *Epidemiology and relevant risk factors*

Chronic suppurative otitis media is a stage of ear disease in which there is chronic infection of the middle ear-cleft (i.e. Eustachian tube, middle ear a nd mastoid) and in which a non-intact tympanic membrane (e.g. perforation or tympanostomy tubes) and discharge (otorrhea) are present.[19] It is a major health problem in many populations around the world, affecting diverse racial and cultural groups.[19] This infection is associated with chronic hearing loss, which may affect development of speech, language, cognition, and school performance.[19]

The etiology and pathogenesis of CSOM usually begins with an acute onset of otitis media. Thus the risk factors that have been associated with acute otitis media may be initially involved, for example, upper respiratory tract infection, Eustachian tube dysfunction, young age, immature or impaired immunologic status, allergies, male sex, race, and environmental factors, such as exposure to smoke.[19]

4. *Clinical presentation*

Acute otitis media always precedes CSOM.[25] Most children with CSOM are afebrile. The patient usually does not complain of severe pain, although there may be intermittent discomfort or a dull earache.[24] The most common physical finding in patients with CSOM is otorrhea through a nonintact tympanic membrane.[24] Conductive and sensorineural hearing loss usually accompany CSOM.[24] It may result from blockage of the external auditory canal by pus and perforation of the tympanic membrane.

5. Approaches to treatment

FLOXIN® Otic is the first and only FDA-approved therapy in patients = 12 years of age for CSOM with a perforated tympanic membrane, and has substantiative literature supporting its use for this condition. Due to its chronicity, CSOM poses specific challenges to treatment. Its potential pathogen mix requires an agent that will eradicate *Pseudomonas aeruginosa,* yet be safe to the exposed middle ear. Augmentin is not effective against *Pseudomonas aeruginosa*. Oral quinolones, which have activity against *Pseudomonas aeruginosa*, are not indicated for pediatric use. Thus, an ototopical quinolone offers a useful combination of efficacy and safety in this indication.

Acute otorrhea in the setting of a respiratory infection or systemic symptomatology probably warrants the use or addition of a systemic antimicrobial with an appropriate antimicrobial spectrum.

C. Acute otitis media with tympanostomy tubes

1. Introduction/Definitions

Acute otitis media (acute middle ear infection) occurs when there is a bacterial or viral infection of the fluid in the middle ear. Ear infections are often associated with respiratory infections or with allergies or enlarged adenoids that block sinuses or Eustachian tubes. When recurrence of otitis media becomes intolerable, the placement of tympanostomy tubes should be considered as the first surgical option.[26]

Insertion of a tympanostomy tube is indicated when long term middle ear ventilation, drainage, or both, are desired.[27] Tympanostomy tube placement may be appropriate in children with more than three episodes of acute otitis media in the past three months or six episodes in the past year.[28] They may also be recommended for any child with structural changes of the Eustachian tube with effusion or bilateral effusion with conductive hearing loss lasting more than 3 months despite treatment with an oral antibiotic.[28]

It is estimated that over two million tympanostomy tubes are placed annually in the United States, primarily in children with chronic or recurrent otitis media refractory to nonsurgical management.[28] Tympanostomy tubes decrease the incidence of acute otitis media in otitis-prone children. Additionally, otorrhea following an episode of acute otitis infection is often painless when a patent tympanostomy tube is present.[28]

2. Microbiology

When acute otitis media occurs in children who have tympanostomy tubes, its pathogenic bacteria differ from those seen in children with an intact tympanic membrane.[4] Pathogens that cause acute otitis media in children with intact membranes usually enter the middle ear from the pharynx via the Eustachian tube.[4] However, in patients with a non-intact tympanic membrane, organisms that colonize the external auditory canal – such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* – are often isolated from middle ear drainage in addition to those commonly seen in acute otitis media.[4]

Mandel[29] and colleagues reported the results of a prospective study of 246 infants and children with tympanostomy tubes. The children were followed for variable lengths of time in three studies conducted at the Children's Hospital of Pittsburgh, Otitis Media Research Center from 1979 until 1990. Cultures of acute otorrhea through tympanostomy tubes were analyzed for organisms and sensitivities. Relevant findings are included in the summary table, Table 6.

Table 6. Distribution of typical pathogens in acute otitis media with tympanostomy tubes

	First Episode			All Episodes		
	101 episodes/108 ears/101 children			178 episodes/194 ears/109 children		
	Pure Culture	Mixed Culture	Total (%)	Pure Culture	Mixed Culture	Total (%)
Streptococcus pneumoniae	16	6	22 (21.8)	24	15	39 (21.9)
Haemophilus influenzae						
ß-Lactamase-negative†	4	3	7 (6.9)	9	12	21 (11.8)
ß-Lactamase-positive†	2	2	4 (4.0)	4	4	8 (4.5)
*Moraxella catarrhalis**	2	4	6 (6.0)	6	9	15 (8.5)
Streptococcus pyogenes	1	1	2 (2.0)	1	3	4 (2.2)
Staphylococcus aureus‡	12	22	34 (33.7)	19	31	50 (28.1)
Pseudomonas aeruginosa	15	11	26 (25.7)	22	15	37 (20.8)
a-Hemolytic *Streptococcus*	0	16	16 (15.8)	5	20	25 (14.0)
Others	16	—	16 (15.8)	34	—	34 (19.1)

† Typeable as well as non-typeable

* ß-Lactamase-positive as well as -negative

‡ 2 ß-Lactamase-negative; 32 ß-Lactamase-positive

Adapted from *Ann Oto Rhin Laryngol.* 1994;103:713-8.

3. Epidemiology and relevant risk factors

"Otitis media is the most common diagnosis made by physicians who provide health care to infants and children, with an increasing prevalence of recurrent otitis media among children in the United States."[27,30] During 1990, there were an estimated 24.5 million physician-office visits for otitis media, while 30 million cases occurred in 1996.[26,31] There is a marked seasonal effect on the prevalence of otitis media with one study demonstrating seasonal variations of 8% (April) to 1.5% (October) in one year old children in the Netherlands.[32] It has also been shown that there is a decreasing prevalence with increasing age of the child.[33,34]

Risk factors for the development of chronic otitis media include: young age, overcrowding, inadequate housing, poor hygiene, lack of breastfeeding, poor nutrition, exposure to cigarette or wood burning smoke, high rates of naso-pharyngeal colonization with potentially pathogenic bacteria, Eustachian tube dysfunction, and inadequate or unavailable health care.[20]

Abnormal functioning of the Eustachian tube plays a significant role in otitis media. The secondary effects of Eustachian tube dysfunction include reflux, aspiration, or insufflation of nasopharyngeal bacteria into the middle ear (caused by crying in an infant, nose blowing, or swallowing when there is nasal obstruction present), leading to mucosal inflammation and infection.[19,35] As the duration of dysfunctional ventilation of an Eustachian tube reaches a variable point, mucosa in the middle ear undergoes a metaplasia from non-fluid producing to fluid producing. This change is reversed with reestablished ventilation.[35]

The placement of tympanostomy tubes may help to re-establish middle ear ventilation. However, tympanostomy tubes are not a cure for the occurrence of acute otitis media. In fact, literature-reported estimates of post tympanostomy otorrhea have ranged from 10% to 74%.[29,36] Acute purulent otorrhea is regarded as evidence of acute otitis media in the presence of tympanostomy tubes.[2,7]

4. *Clinical presentation*

When acute otitis media occurs in children who have tympanostomy tubes, its signs and symptoms differ from those seen in children with an intact tympanic membrane.[4] Fever, systemic signs, and otalgia are seldom seen in children with tympanostomy tubes unless there is a concomitant systemic infection. Otorrhea is the key presenting symptom.[4]

5. *Approaches to treatment*

As with CSOM, ototopical medications are also a principal treatment for acute otitis media with tympanostomy tubes.[37] When a patent tympanostomy tube is present, sterile quinolone drops offer superior safety and efficacy.[1] The spectrum of pathogens seen with a non-intact tympanic membrane requires an agent that will eradicate *Pseudomonas aeruginosa* yet be safe to the exposed middle ear. Systemic antibiotics approved for use in children are not active against *Pseudomonas aeruginosa,* which is an important causative pathogen for the patient with a non-intact membrane.[4]

Acute otorrhea in the setting of a respiratory infection or systemic symptomatology probably warrants the use or addition of a systemic antimicrobial with an appropriate antimicrobial spectrum.

D. Other considerations: Bacterial resistance

A consensus panel convened by the American Academy of Otolaryngology Head and Neck Surgery[1] concluded that in the absence of systemic infections or serious underlying disease, topical antibiotics alone constitute first-line treatment for most patients with CSOM, tympanostomy tube otorrhea, or OE.

Selection of the appropriate ototopical medication is dependent on several factors other than the disease being treated, such as potential side effects, spectrum of activity, potential for ototoxicity, and status of the tympanic membrane.[1]

"The impact of increasing bacterial resistance on otitis media management affects not only medical treatment with antimicrobial agents but also the indications for surgical intervention."[27] Currently the only method of determining whether a child with otitis media has a bacterium that is resistant to standard antimicrobial agents is to perform a tympanocentesis. "[T]ympanocentesis is indicated when a child is critically ill, when there is an unsatisfactory response to antibiotic treatment", and in the presence of suppurative complications.[27]

A study of subjects with CSOM and perforated tympanic membrane measured the concentrations of ofloxacin in otorrhea, serum, and middle ear mucosa after a single dose (0.25 mL in children or 0.5 mL in adults) of topical 0.3% ofloxacin otic solution.[8] Significant concentration of ofloxacin in otorrhea was seen at the initial sampling, 15-30 minutes after dosing (n=16/18). In a subset (n=10) of subjects where otorrhea samples were tested at 4-8 hours post dosing, high concentrations (23.4 -1439.8 μg/g) were still observed. Negligible concentrations of ofloxacin were found in serum after topical administration. Mucosal drug concentrations were highly variable.[8] Further discussion of drug concentrations are addressed in the Pharmacokinetic section of the package insert for FLOXIN® Otic. The measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

It has been postulated that because topical otic antibiotic preparations can achieve local concentrations that are approximately 1000 fold higher than the typical tissue levels seen with

systemic administration of the antibiotic, the development of significant resistance may potentially be diminished.[1]

IV. Place and Anticipated Use of FLOXIN® Otic in Treatment

FLOXIN Otic is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

- **Otitis Externa** due to *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli,* in patients 6 months and older
- **Chronic Suppurative Otitis Media** due to *Staphylococcus aureus, Proteus mirabilis, and Pseudomonas aeruginosa,* in patients 12 years and older with perforated tympanic membranes
- **Acute Otitis Media** with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa,* in pediatric patients one year and older

V. Expected Outcomes of Therapy

Data on expected outcomes of therapy will be outlined in the next section, *Supporting Clinical Information*.

VI. Supporting Clinical Information

A. Introduction

The efficacy and safety of FLOXIN® Otic was determined by eight clinical trials conducted by the pharmaceutical manufacturer.[4-6,7,9] Its efficacy in otitis externa (OE) was determined in two clinical trials in adult subjects and two in children, that compared FLOXIN Otic to Cortisporin Otic (PRTs 02 and 03).[9] Protocols 016, 017 and 020 were designed to examine FLOXIN Otic's effectiveness as once-daily therapy.[5] This information was submitted as a supplemental new drug application (sNDA). Approval for once-daily therapy for OE was received September 2003.

Another pivotal trial evaluated FLOXIN Otic for the treatment of chronic suppurative otitis media (CSOM) with a perforated tympanic membrane (PRT 06).[7] It was not possible to use a direct comparator to FLOXIN Otic for treating CSOM because no topical agent is or was approved in the United States for treating open middle ear infections at the time that the study was conducted. Therefore trial protocol compared a prospective group receiving FLOXIN Otic to a Historical Practice control group and a Current Practice control group.

FLOXIN Otic was also compared to oral Augmentin in subjects with acute otitis media with tympanostomy tubes (AOM TT) (PRT 08).[4] Since Augmentin is not effective against *Pseudomonas aeruginosa*, subjects in whom *Pseudomonas aeruginosa* was isolated as the sole pathogen were excluded from this study and replaced by another subject.

Another small study conducted in subjects with AOM TT was also included for completeness, as the results of this study were used in support of FLOXIN Otic's approval for AOM TT (PRT 07).[2] This trial demonstrated that FLOXIN Otic provided better outcomes as compared to a historical practice group.

Table 7. Summary of FLOXIN® Otic in clinical trials

Study	PRT #	Otic infection	Study Design	N*	Duration	Treatment groups
Jones[9]	02	OE Adults	Multicenter, randomized, evaluator blind	314	10 D	FLOXIN Otic 10 drops BID Cortisporin Otic Solution 4 drops QID
Jones[9]	03	OE Children	Multicenter, randomized, evaluator blind	287	10 D	FLOXIN Otic 5 drops BID Cortisporin Otic Solution 3 drops QID
SNDA[5]	016	OE Adolescents and Adults	Multicenter, randomized, evaluator blind	345	7-10 D	FLOXIN Otic 10 drops QD Cortisporin Otic Suspension 4 drops QID
SNDA[5]	017	OE Children	Multicenter, randomized, evaluator blind	278	7-10 D	FLOXIN Otic 5 drops QD Cortisporin Otic Suspension 3 drops QID
SNDA[6]	020	OE Children Adults	Multicenter, open-label	490 (489 = safety population)	7 D	FLOXIN 5 drops QD FLOXIN 10 drops QD
Agro[7]	06	CSOM	Multicenter, open-label, prospective with historical and concurrent practice control groups	207	14 D	Practice control group FLOXIN Otic 10 drops BID
Goldblatt[4]	08	AOM TT	Multicenter, randomized, parallel group, evaluator blind	474	10 D	FLOXIN Otic 10 drops BID Augmentin 40 mg/kg/day
Dohar[2]	07	AOM TT	Multicenter, open-label, prospective with historical and concurrent practice control groups	143	10 D	Practice control group FLOXIN Otic 5 drops BID

PRT-Protocol Number
*N = total intent-to-treat population for FLOXIN Otic and comparator treatment group
OE – otitis externa
CSOM – chronic suppurative otitis media with perforated tympanic membrane
AOM TT – acute otitis media with tympanostomy tube

B. Twice-daily FLOXIN® Otic for otitis externa[9]

Trial design/objective
Two randomized, evaluator-blind, multi-center trials were performed to compare the safety and efficacy of twice-daily FLOXIN Otic Solution to four times-daily Cortisporin Otic Solution (neomycin sulfate, polymyxin B sulfate, and hydrocortisone) for otitis externa in adults (PRT 02) and children (PRT 03).

Protocol/Setting
Children age = 1 year and = 11 years
Adults age = 12 years
Treatment was assigned according to a computer generated randomized schedule.
Twenty-three primary care and referral ambulatory care sites participated per trial.

Table 8. Treatment groups

	Population	N	Dose	Frequency	Duration
FLOXIN Otic	Adults	158*	10 drops	BID	10 D
	Children	143	5 drops	BID	10 D
Cortisporin Otic	Adults	156*	4 drops	QID	10 D
	Children	144	3 drops	QID	10 D

N: intent to treat population
* In the FDA reviewer's analysis, the number of FLOXIN Otic-treated subjects was reduced to 129, and the number of Cortisporin Otic-treated subjects was reduced to 127. The overall results of the trial were similar in both the original and the adjusted (FDA reviewer's) analyses.

Patient population
The mean age for FLOXIN Otic-treated children was 7.1 ± 2.8 years and for Cortisporin-treated children 7.8 ± 2.8 years. In the clinically evaluable population, the mean ages for adults were 38.2 ± 18.3 years for FLOXIN-treated subjects and 38.9 ± 18.5 years for Cortisporin-treated subjects.

No significant difference in sex, race, laterality of infection, duration and severity of disease, number of organisms, or number of pathogens were noted between treatment groups at enrollment among children or adults.

Treatment period/ assessments

Table 9. Description of evaluation, assessments and bacteriologic assessments

Visit Number Evaluation Description	Investigator assessments	Bacteriologic efficacy assessments
Visit 1 Day 1 Pretreatment or Baseline	NA	NA
Visit 2 Days 3, 4, or 5 During therapy	clinical cure clinical improvement no clinical change clinical exacerbation clinical failure indeterminate	NA
Visit 3 Days 11, 12, or 13 Post therapy visit	clinical cure clinical improvement clinical failure indeterminate	documented eradication presumed eradication persistence colonization superinfection not evaluable
Visit 4 Days 17, 18, 19, or 20 Test of cure	sustained clinical cure subsequent clinical cure clinical failure clinical relapse indeterminate	documented eradication presumed eradication persistence, recurrence superinfection reinfection colonization not evaluable

NA – not applicable

Efficacy analysis

Table 9 above describes clinical and bacteriologic assessments performed by Visit and Study Day. Criteria for clinical efficacy evaluability were considered satisfied if a subject satisfied all inclusion and met no exclusion criteria, received 10 consecutive days of treatment with at least 75% compliance, received no prohibited treatment and returned for the post-therapy and test-of-cure visits, unless withdrawn early because of clinical failure.

Clinical outcome measures

Primary efficacy analysis: Overall clinical efficacy in the clinically evaluable population

Overall clinical responses were assigned as follows:

Cure: Sustained clinical cure or subsequent clinical cure at the test-of-cure visit with 75% of the dose taken

Failure: Clinical relapse at test-of-cure evaluation or clinical failure at any time after receiving at least 3 days of therapy with 75% of the scheduled dose taken

Microbiologic measures

Specimens of otorrhea for bacterial and fungal cultures were collected for culture and antimicrobial susceptibility testing at the pre-therapy visits and at each subsequent visit if there was sufficient otorrhea material for sampling. Subjects were microbiologically evaluable if a valid pathogen was isolated at the pre-therapy visit, a successful culture was obtained (or no appropriate

source was available) at the post-therapy and test-of-cure visits, or a successful culture was obtained at the time of clinical failure.

Results

A total of 314 adults and 287 children were enrolled, of whom 247 adults and 227 children were clinically evaluable. A total of 98 children and 98 adults were microbiologically evaluable. Subject distribution is outlined in Table 10 .

Table 10. Subject distribution

	FLOXIN® Otic			**Cortisporin Otic Solution**		
	Intent to treat	Clinically Evaluable	Microbiologically evaluable	Intent to treat	Clinically Evaluable	Microbiologically evaluable
N – Adults	158	126	48	156	121	50
N - Children	143	116	45	144	111	53

Common pathogens

Pseudomonas aeruginosa and *Staphylococcus aureus* were the most common pre-therapy pathogens. *Enterococcus faecalis* was the third most common pre-therapy pathogen in adults and was also isolated in children.

Table 11. Responses: children and adults

	FLOXIN Otic % (n)	**Cortisporin Otic % (n)**	**P value**
Overall clinical response in intent to treat subjects			
Children			NS
Cure	82% (117)	81% (116)	
Failure	18% (26)	19% (28)	
Adults			NS
Cure	68% (108)	71% (111)	
Failure	32% (50)	29% (45)	
Overall clinical response in clinically evaluable subjects			
Children			NS
Cure	97% (112)	95% (105)	
Failure	3% (4)	5% (6)	
Adults			NS
Cure	82% (103)	83% (101)	
Failure	18% (23)	17% (20)	
Clinical microbiological response in microbiologically evaluable subjects			
Children			NS
Success	98% (44)	100% (53)	
Failure	2% (1)	0	
Adults			NS
Success	85% (41)	88% (44)	
Failure	15% (7)	12% (6)	

NS Not significant, because p> 0.05

Table 12. Overall microbiological response in microbiologically evaluable population*

Response	FLOXIN® Otic	n	Cortisporin	n	P value
Eradication	98%	130	99%	157	NS
Persistence	1%	1	1%	1	NS
Recurrence	1%	1	0	0	NS
Total	100%	132	100%	158	NS

NS Not significant, because p> 0.05

*The n's are derived from the total number of pathogens and isolates identified from both adult and pediatric microbiologically evaluable subjects in the two treatment groups.

Resistant pathogens

Three of 141 pathogens (2%) isolated at the pre-therapy visit in microbiologically evaluable FLOXIN Otic-treated subjects and 13 of 158 pathogens (8%) (p=0.02) isolated at the pre-therapy visit in microbiologically evaluable Cortisporin-treated subjects were resistant to the antibiotic with which the subject was treated.

Subject or guardian satisfaction

Each subject and parent or guardian was to assess discomfort and record compliance with therapy every evening during study drug dosing and document satisfaction with treatment during therapy, and at post-therapy visits. No significant differences between treatment groups were observed with respect to subject or guardian satisfaction at during-therapy and post-therapy visits. Both therapies scored an average of "moderately satisfied" to "very satisfied" throughout the trial. These assessments were made on diary cards, which were not part of the primary data collection instrument (case report form) that was monitored, quality-controlled, and analyzed.

Safety summary

The incidence of adverse events considered by the investigators to be related to treatment was comparable in both treatment groups among children and adults. The most common treatment-related adverse events reported in adults were pruritus (6.3% and 3.8% of FLOXIN Otic- and Cortisporin-treated adults, respectively) and application site reactions (3.8% in each treatment group). The most common treatment-related adverse event reported in children was application site reaction, which occurred in 0.0% and 2.1% of the FLOXIN Otic- and Cortisporin-treated subjects, respectively. There were no statistically significant differences in the incidence of any treatment-related adverse event between treatment arms.

Conclusion

FLOXIN Otic is as effective and well-tolerated as Cortisporin Otic Solution in the management of otitis externa in both children and adults.

- In this study, FLOXIN Otic administered twice daily exhibited efficacy and safety comparable to those of Cortisporin Otic Solution administered four times daily.
- Objective assessments of response to treatment demonstrated a cure in 97% of children and 82% of FLOXIN Otic-treated adults, which was comparable to Cortisporin Otic Solution, but without the need for a steroid.
- Treatment-related adverse events were few and mild and comparable between treatment groups. Pruritus and application site reactions were the most commonly reported events.

C. Once-daily FLOXIN® Otic for otitis externa (PRT 016/017)[5]

Introductory remarks
Protocols 016, 017 and 020 were all used in support of once-daily administration of FLOXIN Otic for the treatment of otitis externa. Protocol 020, described in the next section, was designed and executed to supplement the results obtained from 016 and 017. Specifically, protocol 020 demonstrated that precisely 7 days of therapy was as effective as a 7 to 10 day course, as was allowed in 016 and 017. Secondly, neither protocol 016 nor 017 had enrolled enough subjects in whom *Staphylococcus aureus* was isolated as a baseline pathogen to obtain an indication for that pathogen. Protocol 020 had enrolled adequate subjects with this pathogen to demonstrate the efficacy of once-daily FLOXIN Otic in eradicating this pathogen. Finally, protocols 016/017 used a subject questionnaire in the evaluation of adverse events. This resulted in an unexpectedly high incidence of application site reaction in both the FLOXIN Otic- and Cortisporin Otic Suspension-treated groups. Protocol 020 did not use such a questionnaire and resulted in a significantly lower reported incidence of application site reaction than did 016/017. This led to the FDA-approved wording which explains this effect and is summarized below in Table 19, Safety Summary.

Trial design
Two randomized, active-controlled, evaluator-blinded, multicenter clinical trials were undertaken to demonstrate the safety and efficacy of once-daily administration of FLOXIN Otic for the treatment of otitis externa. One of the studies was conducted in adults and adolescents >12 years of age (Study 016) and the other one in pediatric subjects 9 months to 12 years (Study 017). As the study design and efficacy variables are the same for both studies, results have been combined.

Table 13. Treatment groups

	Population	Randomized N	Dose	Frequency	Duration
FLOXIN Otic	Adults	171	10 drops	Once daily	7-10 D
	Children	140	5 drops	Once daily	7-10 D
Cortisporin Otic	Adults	174	4 drops	Four times daily	7-10 D
	Children	138	3 drops	Four times daily	7-10 D

N: All randomized population

Randomization and treatment groups

Table 14. Subject distribution

	FLOXIN Otic			**Cortisporin Otic Suspension**		
	Intent to treat	Clinically Evaluable	Microbiologically evaluable	Intent to treat	Clinically Evaluable	Microbiologically evaluable
N – Adults	164	122	58	167	119	61
N - Children	135	113	56	133	95	34

Treatment period/assessments
Each subject or parent was instructed to self-administer the study medication as prescribed until End of Therapy (EOT). End of Therapy was predetermined to be day 7 to 9 after initial study drug administration. At EOT the investigator made the determination of adequate or inadequate

response to treatment. If it was determined that adequate treatment had been received, the therapeutic regimen was terminated. If it was determined that adequate treatment had not been received, the subject was instructed to continue study drug through Day 10.

Clinical evaluations were made for both ears and for all subjects. Clinical signs and symptoms for otitis externa (i.e., edema, tenderness, erythema and secretion/exudate) were each graded on a 0-3 scale (four integers). At each visit, the clinical signs and symptoms of otitis externa in the affected ear(s) were scored. The evaluator was blinded to the subjects' treatment assignment for the duration of the study and until database lock. The intent to treat population received at least one dose of study drug.

Clinical outcome measures
Treatment was assessed at EOT and Test of Cure (TOC) visits.

Primary efficacy variable
Sponsor-determined overall clinical response was based on the blinded review of subject profiles and case report form data and incorporated the Sponsor's blinded application of the data conventions for the combined treatment groups of the Clinically Evaluable Sample.

Secondary efficacy measures
Investigator-determined clinical response at EOT and TOC visits.
Investigator-determined overall clinical response
Sponsor-determined overall clinical response for the intent-to-treat sample
For the microbiologically evaluable sample:

- Overall microbiologic response by subject
- Clinical response by subject by pathogen
- Microbiological response by pathogen
- Overall Clinical/Microbiological response

Satisfaction measures
Each subject/parent assessed discomfort and recorded compliance with therapy every evening during study drug dosing and documented their satisfaction with treatment at protocol-driven scheduled visits.

Results
Primary efficacy outcome
Sponsor-determined overall clinical response in the Clinically Evaluable Sample. (Combined data for studies 016 and 017.)

FLOXIN® Otic had a numerically superior cure rate (90.6%) compared with Cortisporin Otic (86.4%) although the difference was not statistically significant (Table 15).

Table 15. Sponsor-determined overall clinical response

Overall Clinical Response	**FLOXIN Otic**	**Cortisporin Otic Suspension**	**Difference in Cure Rate**
Cure	90.6%	86.4%	4.2% p=0.162 95% CI (-2.2, 10.5%)
Failure	9.4%	13.6%	

Secondary efficacy outcomes

Investigator-determined clinical response for overall therapy and at the end of therapy and test of cure visits for the clinically evaluable sample is summarized in Table 16. Clinical cure includes all subjects as clinical cure at EOT who did not return for TOC. Clinical failure includes all subjects categorized as failures at EOT or TOC and subjects categorized as improvement at EOT who did not return for TOC.

Table 16. Investigator-determined clinical response for the clinically evaluable sample

Clinical Response	FLOXIN® Otic	Cortisporin Otic	Difference in cure rate
End of therapy			
Cure	64.3%	50.5%	13.8% p = 0.007 95% CI (4.3, 23.3)
Improvement	32.8%	43.0%	
Failure	3.0%	6.5%	
Test of Cure			
Cure	91.5%	88.4%	3.2% p=0.04 95% CI (-2.9, 9.2)
Failure	5.1%	5.6%	
Missing	3.4%	6.1%	
Overall Clinical Response			
Clinical Cure	91.5%	88.3%	3.2% p=0.264 95% CI (-2.9, 9.2)
Clinical Failure	8.5%	11.7%	

Microbiologic Response

The eradication rate for isolates was high in both treatment groups and comparable for both sensitive and resistant pre-therapy pathogens. However, the proportion of subjects who failed therapy was larger in the Cortisporin Otic group than in the FLOXIN Otic group for both sensitive and resistant pathogens (Table 17). Sensitivity and resistance were determined based on ofloxacin testing in the FLOXIN Otic group, and on neomycin and polymyxin B testing in the Cortisporin Otic group.

Table 17. Summary of Sponsor-determined overall clinical response by susceptibility category of valid baseline pathogen to drug received

	FLOXIN Otic N=114*	Cortisporin Otic N=95
Sensitive pathogens		
Clinical Cure	95 (91.3%)	68 (88.3%)
Clinical Failure	9 (8.7%)	9 (11.7%)
Total	104 (100.0%)	77 (100.0%)
Resistant Pathogens		
Clinical Cure	8 (100%)	15 (83.3%)
Clinical Failure	0 (0%)	3 (16.7%)
Total	8 (100.0%)	18 (100.0%)

*Two FLOXIN Otic-treated subjects were missing a clinical response assessment at Test of Cure.

Microbiological eradication
FLOXIN® Otic and Cortisporin Otic showed comparable microbiological eradication rates for each pathogen. In the FLOXIN Otic group, 142 pre-therapy pathogens were isolated from target ears. Of these, 135 isolates were tested for ofloxacin susceptibility. In the Cortisporin group, 129 pre-therapy pathogens were isolated from target ears. Of these, 126 were tested for susceptibility. Among these 135 and 126 isolates, both treatments showed 100% eradication of the pre-therapy pathogen, with the exception of *Pseudomonas aeruginosa*, for which persistence was noted in 1/94 isolates, and *Streptococcus viridans*, for which persistence was noted in 1/7 isolates in the FLOXIN Otic group; and 2/79 isolates of *Pseudomonas aeruginosa*, in the Cortisporin group.

Sponsor-determined overall clinical response by single or multiple valid baseline pathogens
In FLOXIN Otic-treated subjects, the cure rate was similar whether subjects had multiple or a single baseline pathogen (91.7% and 92.2%, respectively). For Cortisporin Otic-treated subjects, the cure rate was less in subjects with multiple baseline pathogens compared to a single baseline pathogen (77.8% and 91.2%). The overall microbiological eradication rate was 98.2% for FLOXIN Otic, and 96.7% for Cortisporin Otic.

Summary of microbiologic analysis
In the microbiologically evaluable sample, the overall clinical/microbiological response showed FLOXIN Otic to have a comparable overall success rate to that of Cortisporin Otic (Table 18).

Table 18. Overall Combined Clinical/Microbiologic Response in the microbiologically evaluable sample

Overall Combined Clinical/ Microbiologic Response	FLOXIN Otic	Cortisporin Otic	Difference in Cure Rate
Success	92.0%	87.4%	4.7% p=0.266 95% CI (-4.6, 14.0)
Failure	8.0%	12.6%	

Safety summary

Protocol 016
In PRT-016, a total of 247 adverse events were reported by 79/171 (46.2%) FLOXIN Otic and 84/173 (48.6%) Cortisporin Otic subjects. No statistically significant differences in the frequency of AEs between treatment groups were noted. There were no SAEs reported in the FLOXIN Otic group. No deaths occurred during this study. A total of 9/171 (5.3%) FLOXIN Otic and 12/173 (6.9%) Cortisporin Otic subjects discontinued due to AEs, most of which were considered not related to study treatment.

Protocol 017
In PRT-017, a total of 190 AEs were reported by 63/139 (45.3%) FLOXIN Otic and 60/138 (43.5%) Cortisporin Otic subjects. There were no deaths or serious AEs reported during this study. A total of 5/139 (3.6%) FLOXIN Otic and 4/138 (2.9%) Cortisporin Otic subjects were discontinued due to AEs; none of which was considered related to study treatment.

When safety data from both protocols were combined, the following treatment-related adverse events occurred in two or more of the subjects.

Table 19. Treatment-related adverse events occurring in two or more subjects in Protocols 016 and 017

Adverse Event	Incidence Rate Studies 016/017
Application site reaction	16.8%*
Pruritis	1.2%
Earache	0.6%
Headache	0.3%

*An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once-daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

Subject/Parent satisfaction

Satisfaction was measured by a nine-item Satisfaction Questionnaire, which was constructed to measure four components of satisfaction: Ease of Administration, Relief from Symptoms, Functioning, and Overall Satisfaction. Results were obtained at both the End of Therapy and Test of Cure time points for both studies, 016 and 017.

A published analysis of subject/parent satisfaction in this once-daily dosing regimen highlighted the differences in satisfaction ratings between the two studied products.[37] Diary cards were used to obtain these data. The total satisfaction score for both adult and pediatric study-groups was higher for FLOXIN® Otic treatment than for Cortisporin Otic treatment ($p<0.0001$ for both comparisons). Compared to the Cortisporin groups, the FLOXIN Otic groups in both studies indicated greater total satisfaction, greater satisfaction with ease of administration, and greater overall satisfaction. Lastly, the treated subjects in the FLOXIN Otic groups were more compliant, as measured by percentage of doses administered, with the once-daily regimen than were the treated subjects who received the four times-daily Cortisporin Otic regimen in both studies.[37]

Conclusion

- The combined data from studies in both children and adults demonstrate that FLOXIN Otic once daily is comparable in efficacy to Cortisporin Otic administered four times daily, with a FLOXIN Otic overall combined clinical/microbiological response rate of 92.0%.
- In the microbiologically evaluable sample, both Sponsor-determined overall clinical response and Investigator-determined overall clinical response showed FLOXIN Otic to have a comparable cure rate to that of Cortisporin Otic.
- The pathogen eradication rate was very high in both treatment groups, both overall and for those pathogens that were sensitive; resistance did not seem to adversely affect clinical outcome in either treatment group, although the sample sizes were small.
- Subjects and parents both reported higher total satisfaction scores for FLOXIN Otic as compared to Cortisporin Otic.

D. Once-daily FLOXIN® Otic for otitis externa (PRT 020)[6]

Trial design

A Phase III, multi-center, open-label trial was conducted in North America and Central America. Subjects were to have a clinical diagnosis of otitis externa presumed to be of bacterial origin and were each to be treated with FLOXIN Otic.

Protocol/Setting
Children age 6 months to 13 years
Adults = 13 years

FLOXIN Otic was administered as either 5 drops QD or 10 drops QD, depending on population subset, for exactly 7 days.

Forty-three centers in North America and fifteen centers in Central America participated.

Patient Population
The mean age for FLOXIN Otic-treated children was 8.0 years. The mean age for FLOXIN Oticreated adults was 36.1 years.

Treatment period/assessments

Table 20. Description of evaluation, assessments and bacteriologic assessments

Visit Number Evaluation Description	Investigator assessments	Bacteriologic efficacy assessments
Visit 1 Day 1 Pretreatment or baseline	NA	NA
Visit 2 Day 7	clinical cure clinical improvement clinical failure indeterminate	documented eradication presumed eradication documented persistence presumed persistence recurrence superinfection colonization
Visit 3 **End of treatment** **(EOT)**	sustained clinical cure subsequent clinical cure clinical failure	documented eradication presumed eradication documented persistence presumed persistence recurrence
Test of cure **(TOC)** Days 7-10 Post Treatment	clinical cure clinical failure	<u>Primary Bacteriological Response Categories</u> documented eradication presumed eradication documented persistence presumed persistence recurrence <u>Secondary Bacteriological Response Categories</u> superinfection colonization

NA – not applicable

Efficacy analysis
Criteria for clinical efficacy were considered satisfied if a subject received 7 consecutive days of treatment with at least 75% compliance.

Clinical outcome measures
Primary efficacy variable is the Sponsor-Determined Overall Clinical Response, determined from overall evaluation of the data contained in the electronic case report form (eCRF).

Each of four OE signs and symptoms (erythema, edema, tenderness and secretion/exudate) was evaluated on a four-point scale (3 = severe, 2 = moderate, 1 = mild, 0 = absent) prior to initiation of therapy. Further, a total score of at least six, derived by adding the score from each of these individual measures, was required at study entry.

Overall clinical responses were assigned as follows:

End of Treatment Clinical Response

Clinical Cure	Complete resolution of signs and symptoms with the exception of mild erythema, edema, or tenderness, which may have been present. Total score = 1
Clinical Improvement	Decrease in total signs/symptoms score from baseline without complete resolution (total score of 1 or higher, not including a score of 1 for erythema, edema, or tenderness).
Clinical Failure	Persistence or an increase of signs and/or symptoms (after a minimum of 3 days of treatment), severe enough to warrant a change in antimicrobial therapy.
Indeterminate	Discontinued (prior to a minimum of 3 days of treatment) or lost to follow-up.

Test of Cure Clinical Response

Clinical Cure: Sustained clinical cure, which is clinical cure at both end of treatment and test of cure evaluations, or subsequent clinical cure, which is clinical improvement at end of treatment with clinical cure at test of cure.

Clinical Failure: Recurrence or persistence of signs and symptoms of otitis externa during the 7-10 days post-treatment follow-up period requiring additional antimicrobial therapy.

Microbiologic measures

Specimens of otorrhea for bacterial and fungal cultures were collected for culture and antimicrobial susceptibility testing at the pre-therapy visits and at each subsequent visit.

Subjects were excluded from the Microbiologically Evaluable Sample for the following reasons:

Not clinically evaluable, and/or
No baseline pathogens

Results

A total of 489 adults and children received at least one dose of ofloxacin otic solution, of whom 439 (89.6%) were clinically evaluable. A total of 253 were microbiologically evaluable.

Table 21. Sponsor-determined overall clinical response

	Number	**%**
Clinical cure	398/439	90.7%
Microbiologically evaluable	226/242	93.4%

Table 22. Overall by-subject pathogen eradication rate

	Number	**%**
Overall by-subject pathogen eradication rate	242/253	95.7%

Table 23. Overall eradication rate by pathogen

Pathogen	Number	%
S. aureus	31/32	96.9%
*P. aeruginos*a	153/158	96.8%
K. pneumoniae	24/24	100%
E. faecalis	22/22	100%
E. coli	12/13	92.3%
S. maltophilia	12/12	100%
P. mirabilis	11/12	91.7%
E. cloacae	11/11	100%

Within the microbiologically evaluate sample, the proportion of subjects cured with resistant pathogens (24/29; 82.8%) was nearly as high as the proportion of subjects cured having sensitive pathogens (313/343; 91.3%). (Due to subjects being counted for each baseline isolate, subjects with multiple baseline pathogens in the trial are counted more than once in this clinical outcome analysis.)

Safety summary

A total of 178 adverse events were reported by 119/489 (24.3%) subjects regardless of relationship to study drug. Of subjects reporting adverse events, most 104/119 (87.4%) reported adverse events that were mild or moderate in severity. There were no reports of serious adverse events.

Out of a total of 489 subjects, twenty-six (26) treatment-related adverse events were reported by 15 subjects (3.1%), while treatment-related application site reactions were observed in only 3 subjects (0.6%). There were 6 subjects who discontinued from the study for adverse events (1.2%), only one of which (an application site reaction of moderate severity) was considered study drug-related.

Table 24. Treatment-related adverse events seen in two or more subjects from Protocol 020

Adverse Event	Incidence Rate Study 020
Application site reaction	0.6%
Pruritis	1.0%
Earache	0.8%
Dizziness	0.6%
Headache	0.2%

In once-daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

Conclusion

The results of this Phase III, multi-center, open-label study demonstrated the efficacy of a once-daily, 7-day regimen of FLOXIN® Otic 0.3% solution in the treatment of otitis externa, including subjects with infections due to *P. aeruginosa* and/or *S. aureus*. In addition, FLOXIN Otic had eradication rates of 91.7% to 100% in subjects with the following pathogens: *E. faecalis, E. cloacae*, *E. coli, S. maltophilia, K. pneumoniae* and *P. mirabilis*. FLOXIN Otic was equally effective and well tolerated by pediatric and adolescent/adult subjects with otitis externa.

E. Chronic suppurative otitis media with perforated tympanic membrane[7]

Trial design and protocol
A multi-center, open-label, prospective trial was performed to determine the efficacy of FLOXIN® Otic solution to treat chronic suppurative otitis media (CSOM), a disorder characterized by chronic inflammation of the middle ear and mastoid, purulent otorrhea, and a persistent perforation of the tympanic membrane.[38] The study was conducted in subjects ≥ 12 years of age.

Purulent otorrhea was defined as any purulent or mucopurulent secretion from the external canal through a perforated tympanic membrane.

Protocol
It was not possible to use a direct comparator for FLOXIN Otic in this clinical trial, because no topical agent was approved in the United States for treating middle ear infections. There were few data in the literature regarding clinical efficacy in subjects treated with other regimens. Therefore, a retrospective review of records from historical practice control (HPC), and the identification of a concurrent practice control cohort (CPC), served as the "comparator arms" for this study.

Treatment groups

Prospective arm - FLOXIN Otic
10 drops (0.5 mL) BID for 14 da

	Subjects		
Enrolled	ITT	Clin. Eval.	Micro. Eval.
207	207	162	99

ITT intent to treat

Control Group Cohorts	All Subject	Subjects with Final Follow-Up Visits
Historical Practice Controls [HPC]*	220	185
Current Practice Controls [CPC]*	63	54

*The various treatments used by these subjects were not recorded.

There were a total of 207 subjects enrolled and 162 clinically evaluable subjects at 27 centers in the United States and Central America in the prospective, FLOXIN Otic-treated group. There were 99 microbiologically evaluable subjects.

Patient population-prospective group
The demographic characteristics of the FLOXIN Otic treated group were not significantly different from those of the other two (control) treatment groups with respect to age, sex, or age and sex distribution. Clinically evaluable subjects ranged in age from 12 to 87 years with a mean age of 45 years for FLOXIN Otic and HPC subjects and 49 years for CPC subjects.

Assessments

Subjects were evaluated at four points during the study:

Visit 1	baseline and treatment initiation visit, day one
Visit 2	during therapy (days 4 to 6)*
Visit 3	post therapy (days 15 to 17)*
Visit 4	follow-up evaluation (days 21 to 24)*

*Each time interval is measured with respect to day one, when dosing commenced.

The same investigator evaluated each subject at every visit using the same methods. The most severely infected ear at baseline, or the right ear if both ears were equally affected, was designated the target ear.

Adverse events were observed by investigators or were spontaneously reported during visits 2, 3, and 4. Daily treatment diaries were reviewed for adverse events. Information for bitter taste was specifically solicited after the first dose and was recorded as an adverse event.

Clinical outcome measures

The overall clinical end points:

Cure	dry ear at visit 4
Failure	no dry ear at any time after at least 3 days of therapy with at least 75% of the scheduled total study dose taken

The primary microbiologic outcomes for FLOXIN® Otic were:

- Complete eradication of baseline pathogens (documented by repeat cultures) OR
- Presumed eradication of baseline pathogens (based on sustained clinical cure, absence of otorrhea but without repeat cultures)

No microbiological evaluations were made for the Historical Practice (HPC) and Current Practice control (CPC) subjects because they were not studied prospectively, and routine culturing with sensitivity testing cannot be assured as part of naturalistic case management.

Overall clinical/microbiologic evaluations

Overall clinical/microbiologic success was defined as clinical cure, with either complete eradication of baseline pathogens (as documented by repeat cultures from specimens taken at any post-baseline visit at which otorrhea was present) or presumed eradication (based on sustained clinical cure without repeat culture, in the absence of otorrhea). All other subjects who were evaluable for microbiologic and clinical efficacy and were not classified successes were considered failures.

Microbiologic evaluation

At baseline and at any subsequent visit at which otorrhea was present the external ear canal was cleansed and a specimen of otorrhea was taken for Gram's staining. Aerobic bacterial cultures and fungal and mycobacterial cultures were performed.

No microbiologic evaluations were performed for the HPC or CPC subject groups because they were not studied prospectively; neither were adverse events recorded for the HPC or CPC subjects, since they were treated with a variety of different therapies.

Results

Primary efficacy end points

There was a rapid improvement from baseline clinical status at each successive visit. For clinically evaluable FLOXIN® Otic-treated subjects, clinical improvement was seen in 88% (143/162) of subjects at visit 2, 96% (156/162) of subjects at visit 3, and 94% (149/158) at visit 4. (Subjects who were treatment failures at visit 3 did not return for final follow-up evaluation at visit 4.)

Table 25. Clinical cure rates

	FLOXIN Otic (N=162)	**HPC subjects** (N=185)	**CPC subjects** (N=54)
Clinical cure	91% (148)	67% (124)	70% (38)
p value compared to FLOXIN Otic		p< 0.001*	p< 0.001
p value compared between HPC and CPC subjects		p=0.713	

HPC - historical practice control group

CPC - current practice control group

* In comparing the HPC group to the FLOXIN Otic group, it was recognized that CSOM treatment, causative pathogens and response of pathogens to treatment may have changed over the course of 4 years and comparison of outcomes should serve as a general guide only.

Table 26. Overall microbiologic and clinical response to FLOXIN Otic by pathogen >1 isolate

	Overall Microbiologic Response		**Overall Clinical Response**	
	Isolates N	**Eradication %**	**Clinical Cure** N (%)	**Failure** N (%)
S. aureus	40	100	36 (90)	4 (10)
P. aeruginosa	39	100	38 (97)	1 (3)
P. mirabilis	15	100	15 (100)	
E. faecalis	7	100	6 (86)	1 (14)
E. cloacae	4	100	4 (100)	
K. oxytoca	4	100	4 (100)	
S. marcescens	4	100	4 (100)	
A. faecalis	3	100	3 (100)	
C. freundii	3	100	3 (100)	
M. morganii	3	100	3 (100)	
C. diversus	2	100	2 (100)	
H. influenzae	2	100	1 (50)	1 (50)
K. ozaenae	2	100	2 (100)	
K. pneumoniae	2	100	2 (100)	
P. vulgaris	2	100	2 (100)	
P. rettgeri	2	100	2 (100)	
S. pneumoniae	2	100	2 (100)	

Satisfaction ratings

A treatment diary was distributed to each subject at the first visit and reviewed at each subsequent visit. Subjects or their caregivers rated satisfaction with therapy as "very satisfied," satisfied," dissatisfied," or "very dissatisfied."

Satisfaction ratings in subjects' treatment diaries demonstrated that 90% (181/207) of the intentto-treat population were either "satisfied" or "very satisfied" with FLOXIN® Otic therapy. Five percent (11 of 207) subjects or their parents were dissatisfied at the end of treatment (visit 3).

Safety summary

Safety analyses were performed only for subjects who received at least one dose of FLOXIN Otic. No information was recorded from the medical records of HPC or CPC subjects because adverse events had not been consistently recorded, and further, these subjects had received a variety of different therapies for CSOM other than FLOXIN Otic.

The most commonly reported adverse event was taste perversion, occurring in 17% of subjects. Earache occurred in 6% and headache in 5%, while dizziness and pruritus each occurred in 3% of subjects. Tinnitus and URI each occurred in 2% of subjects.

Only four subjects experienced adverse events characterized as severe and none were reported in more than one subject. Five subjects (2.4%) discontinued study medication because of adverse events, one for each of the following: urticaria, paresthesia, tachycardia, vertigo, dizziness, and nausea.

No clinically significant changes in vital signs occurred during the study. No life-threatening adverse events were observed and no deaths occurred during treatment or within 30 days of the last dose.

Conclusion

These results show that FLOXIN Otic Solution is effective for treating chronic suppurative otitis media with a perforated tympanic membrane.

- The overall clinical response of cure in FLOXIN Otic-treated subjects of 91% was significantly greater than the responses to therapies used in either the historical practice (67%) or current-practice (70%) groups.
- The overall microbiologic response showed FLOXIN Otic to be effective in eradicating baseline pathogenic organisms in 100% of evaluable subjects. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most commonly encountered pathogens, followed by *Proteus mirabilis* and *Enterococcus faecalis.*
- Satisfaction ratings in subjects' treatment diaries demonstrated that 90% of the intent-to-treat population were either "satisfied" or "very satisfied" with FLOXIN Otic therapy.
- Overall, there was a low incidence of treatment related adverse events.
- FLOXIN Otic is the only FDA approved treatment for CSOM.

F. Acute otitis media with tympanostomy tubes[4]

Trial design and protocol

A multi-center, randomized, parallel-group, evaluator-blind study was undertaken to compare the safety and efficacy of FLOXIN® Otic 0.3% solution to Augmentin oral suspension in children with tympanostomy tubes and acute purulent otorrhea.

There were 36 study centers in the United States and one in Chile. Each center had an unblinded study coordinator. Physicians who served as evaluators performed each study procedure without knowledge of a subject's treatment assignment. Audiologists also had no knowledge of a subject's therapy group.

A total of 474 enrolled subjects in the study were considered valid for the intent-to-treat analysis; 228 treated with FLOXIN Otic and 246 treated with Augmentin. One hundred forty (140) subjects treated with FLOXIN Otic and 146 treated with Augmentin comprised the clinically evaluable population. The most common reasons for exclusion were isolation of *Pseudomonas aeruginosa* as the sole pathogen (since the organism is not sensitive to Augmentin) and protocol noncompliance.

Treatment groups

FLOXIN Otic 0.50 mL (10 drops) twice daily
Augmentin oral suspension 13.3 mg/kg three times daily (for a total of 40 mg/kg/day)

10 consecutive days of therapy

If an Augmentin-treated subject under 2 years of age developed diarrhea, the dose was reduced to 25 mg/kg/day.

Audiometry assessment
Subjects were eligible for audiometry assessment if they were enrolled at a site selected and qualified for conducting audiometry testing and were between 4 and 12 years of age. Subjects were excluded from audiometry assessment if they had a diagnosis of sensorineural hearing impairment.

Patient population

Forty-seven of 140 (34%) FLOXIN Otic-treated subjects were < 2 years of age, while 66% of subjects were 2-11 years of age; 55% were male. In the Augmentin-treated group, 43% of subjects were < 2 years of age while 57% were 2-11 years of age; 61% were male.

There were no statistically significant differences between the FLOXIN Otic-treated and the Augmentin-treated groups, either in their respective clinically evaluable or intent-to-treat populations with respect to mean age, sex, race distribution, medical history or vital signs. At baseline, mean otorrhea scores were not statistically significantly different between the treatment groups for either clinically evaluable or intent-to-treat populations.

Efficacy analysis

Subjects who had complete resolution of otorrhea at visit four were classified as clinical cures and all others were classified as clinical failures. In cases of bilateral infection at baseline, resolution of otorrhea in the target ear alone, with persistence in the nontarget ear, was counted as failure.

Subjects who were withdrawn prior to the final visit or who may have missed some doses, were considered evaluable if they received at least 75% of the scheduled 10-day treatment.

The microbiologically evaluable population included all clinically evaluable subjects with valid pathogens isolated at baseline, with culture obtained at visits three and four if culturable otorrhea was still present at those times, or with successful culture obtained when clinical failure was determined.

Treatment assessments
Subjects were evaluated at four points in the study.*

Visit 1	pretreatment or baseline (day 1)
Visit 2	during therapy (day 4 to 6)
Visit 3	post-therapy (day 11 to 13)
Visit 4	test of cure (day 17 to 20)

*Each time interval is measured with respect to day one, when dosing commenced.

At each visit the characteristics of otorrhea, the presence or absence of otorrhea odor and the degree of granulation tissue were assessed and recorded using relative numerical scores. Otorrhea was scored on a four-point scale of 0 to 3:

absent (0)
serous (1)
mucopurulent (2) or
purulent (3)

Clinical outcome measures

Primary efficacy end points:
Overall clinical response

Cure or failure was defined as the absence or presence of otorrhea, respectively.

Microbiologic evaluations:
A specimen of otorrheal fluid was taken for bacterial and fungal cultures from the lumen of each draining tympanostomy tube at baseline and at subsequent visits. Aerobic cultures and fungal and mycobacterial growth determinations by culture were performed. Gram stains were also performed on otorrhea specimens taken from subjects at the time of clinical failure.

If cultures obtained at the final follow-up visit showed eradication of all valid baseline pathogens or if a sustained clinical cure with no pathogen source at final follow-up allowed presumption of eradication, the result counted as overall microbiologic success.

Auditory function evaluations
The primary measure of drug-related ototoxicity was a change in the ability to detect bone-conducted sound.

Results

Primary efficacy end points

Among the clinical evaluable subjects, an overall clinical cure was achieved in 76% of the FLOXIN® Otic-treated subjects and 68% of the Augmentin-treated subjects (difference not statistically significant). There were no statistically significant differences between the two groups with respect to the clinical responses reported at visits two, three and four. A summary of clinical response is provided in Table 27.

Table 27. Clinical response in clinically evaluable subjects

Visit	Response	FLOXIN Otic N (%)	Augmentin N (%)	p value
2	Clinical improvement No clinical change Clinical failure	116 (84%) 21 (15%) 1 (1%)	122 (86%) 19 (13%) 1 (1%)	0.664
3	Clinical improvement No clinical change Clinical failure	115 (84%) 2 (2%) 20 (15%)	112 (78%) 1 (1%) 31 (22%)	0.192
4	Clinical cure Clinical failure	107 (89%) 13 (11%) 120	101 (89%) 12 (11%)	0.966
Overall	Cure Failure	107 (76%) 33 (24%)	101 (68%) 45 (31%)	0.169

Microbiologic efficacy and response

There were significantly higher eradication rates in the FLOXIN Otic-treated group than in the Augmentin group for *Staphylococcus aureus* and for *Pseudomonas aeruginosa*. Equivalent eradication rates occurred in the two treatment groups for *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis*. All the remaining 27 baseline pathogens of other species from FLOXIN Otictreated subjects were eradicated, compared with 62% (13/21) of those from Augmentin-treated subjects.

Three pathogens were not eradicated in the FLOXIN Otic arm of the study, compared to 30 not eradicated in the Augmentin arm. Overall microbiologic eradication rate was 96% in the FLOXIN Otic arm of the study, compared to 67% in the Augmentin arm. Tables 28 and 29 summarize the microbiological efficacy by pathogen and response by subject.

Table 28. Overall eradication rate by most common pathogen*

	Overall Eradication Rate		
Pathogen	**Ofloxacin**	**Augmentin**	**95% C.I.**
Streptococcus pneumoniae	100% (36/36)	87% (33/38)	(-0.3,26.6)
Haemophilus influenzae	93% (26/28)	77% (30/39)	(-3.4,35.3)
Staphylococcus aureus	96% (27/28)	48% (12/25)	(23.9,73.0)
Moraxella catarrhalis	93% (13/14)	90% (9/10)	(-28.7,34.4)
Pseudomonas aeruginosa	100% (9/9)	43% (3/7)	(7.8,100)

*Subjects in whom *Pseudomonas aeruginosa* was isolated as the sole pathogen were dropped from the study and replaced by another subject, since the organism is not considered sensitive to Augmentin and is not approved for this indication.

Table 29. Microbiologic response by subject

Visit	Response	FLOXIN® Otic N (%)	Augmentin N (%)	p value
3	Eradication	82 (99%)	67 (72%)	< 0.001
	Persistence	1 (1%)	26 (28%)	
4	Eradication	69 (97%)	63 (91%)	0.122
	Persistence	0	1 (1%)	
	Recurrence	2 (3%)	4 (6%)	
	Reinfection	0	1 (1%)	
Overall	Eradication	80 (96%)	62 (67%)	< 0.001
	Persistence	1 (1%)	26 (28%)	
	Recurrence	2 (2%)	4 (4%)	
	Reinfection	0	1 (1%)	

Pathogen resistance

Of 142 pathogens isolated from otorrhea specimens at baseline in the FLOXIN Otic-treated group, only one was resistant to FLOXIN Otic. Of 140 baseline pathogens in the Augmentintreated group, 19 (14%) were resistant to Augmentin. Five sensitive baseline pathogens isolated from Augmentin-treated subjects acquired resistance during the study.

Auditory function evaluations

Audiometry analyses were done on 30 FLOXIN Otic- and 26 Augmentin-treated subjects who were audiologically evaluable. No subject in either treatment arm displayed treated-related ototoxicity. Nineteen (68%) of the FLOXIN Otic-treated subjects and nine (35%) of the Augmentin-treated subjects showed improvement in detecting air-conducted sound, which probably reflected the improvement in middle ear status with treatment.

Parent or guardian satisfaction

Significantly more parents or guardians of the FLOXIN Otic-treated subjects were very satisfied with treatment at visit three (end of therapy) than were parents or guardians of Augmentin-treated subjects (55% vs. 40%; p=0.002).

Safety summary

A significantly lower percentage of FLOXIN Otic-treated subjects (6%, 13/228) than of Augmentin-treated subjects (31%, 77/246) experienced adverse events that were considered related to study medication (p< 0.001). A significantly higher percentage of Augmentin-treated subjects experienced treatment-related diarrhea (27% vs. 1%; p< 0.001), treatment-related rash (5% vs. 1%; p=0.022), or treatment-related moniliasis (3% vs. 0%; p=0.015). Nine (4%) of FLOXIN Otic-treated and 19 (9%) of Augmentin-treated subjects experienced adverse events that resulted in discontinuation of study medication.

Conclusion

These results show that FLOXIN® Otic is as effective as Augmentin oral therapy for producing clinical cure in subjects with acute otitis media with tympanostomy tubes.

- An overall clinical cure – the absence of otorrhea and eradication of baseline pathogens – was found in 76% of FLOXIN Otic-treated subjects compared to 68% of the Augmentin-treated subjects. (Subjects in whom *Pseudomonas aeruginosa* was isolated as the sole pathogen were dropped from the study and replaced by another subject, since the organism is not considered sensitive to Augmentin and is not approved for this indication.)
- The overall microbiologic eradication rate was 96% in FLOXIN Otic-treated subjects, and 67% in Augmentin-treated subjects, $p < 0.001$.
- Treatment-related adverse events occurred in statistically significantly lower percentages of FLOXIN Otic-treated subjects (6% vs. 31%, $p< 0.001$).
- A significantly lower percentage of FLOXIN Otic-treated subjects (6%) than of Augmentin-treated subjects (31%) experienced adverse events that were considered related to study medication ($p< 0.001$).

G. Acute otorrhea in children with tympanostomy tubes[2]

Trial design
A multi-center study with an open-label, prospective ofloxacin arm and retrospective historical practice and current practice arms to determine the safety and efficacy of ofloxacin otic solution in the treatment of acute otorrhea in children with tympanostomy tubes.

Protocol
There were 27 study centers of ear, nose and throat pediatric and general practice clinics and office-based practices participating in this study.

Subjects in whom treatment failed at visit 2 or visit 3 had their final study procedures performed at that time and did not return for visit 4.

Treatment groups
Prospective arm: ofloxacin otic 0.3% solution, 5 drops (0.25 mL) twice daily for 10 days
Current practice group: data for the current practice group were obtained by reviewing records of subjects treated at the study centers during the time the prospective ofloxacin arm was ongoing who did not wish to or could not participate in the ofloxacin arm

Historical practice group: review of medical records of subjects who had been treated before initiation of the prospective arm in the same institutions

	Subjects			
Prospective arm – FLOXIN® Otic 5 drops (0.25 mL) BID for 10 days	Enrolled	ITT	Clin. Eval.	Micro. Eval.
	226	226	143	107

ITT – intent-to-treat

Control Group Cohorts	All Subjects	Subjects with Final Follow-Up Visits
Historical Practice Controls [HPC]*	309	218
Current Practice Controls [CPC]*	68	48

*The various treatments used by these subjects were not recorded.

Patient population
Demographic characteristics of the ofloxacin group were similar to those of the historical practice and current practice treatment groups with respect to age and gender. The mean age in the ofloxacin group was 3.6 years. In each study population, there were more male than female subjects.

Treatment assessments
Subjects were evaluated at four points in the study.

Visit 1	pretreatment or baseline (day 1)
Visit 2	during therapy (day 4 to 6)
Visit 3	post-therapy (day 11 to 13)
Visit 4	test of cure (day 17 to 20)

At each visit the characteristics of otorrhea (absent, serous, mucopurulent, or purulent), the presence or absence of otorrhea odor, and the degree of granulation tissue were assessed and recorded with relative numerical scores.

Signs of otorrhea were recorded and evaluated as representing cure (resolution of otorrhea), improvement (visits 2 and 3 only), no change (visits 2 and 3 only) or failure (presence of otorrhea).

Clinical outcome measures

Primary efficacy end points:
The overall clinical responses were classified as cure or failure and were defined as the absence (dry ear) or presence (not dry ear) of otorrhea.

Medical records of subjects in the historical practice and current practice groups were reviewed to determine whether the subjects could be classified as "cure" or "failure". If the records contained insufficient information, subjects were considered not clinically evaluable. If a subject could not be reached, outcome was assumed to be failure. If a subject could not remember the outcome, it was assumed to be dry ear (cure).

Microbiologic evaluations:
A specimen of otorrheal fluid was taken for bacterial and fungal cultures from the lumen of each draining tympanostomy tube at baseline and at subsequent visits. Aerobic cultures and fungal and mycobacterial growth determination by culture were performed. Gram stains were performed on otorrhea specimens taken from subjects at the time of clinical failure.

If cultures obtained at the final follow-up visit showed eradication of all valid baseline pathogens or if a sustained clinical cure with no pathogen source at final follow-up allowed presumption of eradication, the result counted as overall microbiologic success.

Results

A total of 226 FLOXIN® Otic-treated subjects were included in the intent-to-treat population. There were 83 subjects in the FLOXIN Otic group who were excluded, leaving 143 clinically evaluable subjects. There were 107 microbiologically evaluable subjects.

Table 30. Overall clinical cure rates in the clinically evaluable population*

	FLOXIN® Otic (N=143)	**HPC subjects** (N=218)	**CPC subjects** (N=48)
Clinical cure	85% (121)	64% (140)	71% (34)
P value compared to FLOXIN Otic		P< 0.001	P=0.03

HPC - historical practice control group
CPC - current practice control group
*Includes only HPC subjects and CPC subjects that had an approved follow-up visit

Microbiologic response
A total of 107 subjects in the ofloxacin groups were microbiologically evaluable. Microbiologic evaluations were not conducted for subjects in the retrospective arms of the study.

Eradication of baseline pathogens occurred in 103 (96.3%) of microbiologically evaluable subjects in the ofloxacin group. *Pseudomonas aeruginosa* persisted in 2 microbiologically evaluable subjects, *Streptococcus pneumoniae* persisted in 1 subject, and a superinfection (eradication of baseline pathogen with the presence of a new pathogen) occurred in one subject.

Table 31. Microbiologic and clinical response by pathogen with 15 or more isolates (n=isolates)

	Microbiologic Response %		**Clinical Response %**	
	Eradication	Persistence	Cure	Failure
Pseudomonas aeruginosa (n=34)	94	6	88	12
Haemophilus influenzae (n=30)	100	0	83	17
Streptococcus pneumoniae (n=29)	97	3	83	17
Staphylococcus aureus (n=26)	100	0	96	4
Moraxella catarrhalis (n=15)	100	0	87	13

Satisfaction rating
In the intent-to-treat population (N=226), most parents or guardians were either "satisfied" or "very satisfied" with treatment at visits 2 (85%) and 3 (81%).

Safety summary
A total of twenty-nine subjects (13%) experienced an adverse event that investigators determined to be either possibly or probably related to the study drug, most of which were mild to moderate in severity. Only 3 subjects (1%) experienced treatment-related adverse events considered by investigators to be severe – halitosis, taste distortion, and rash. Table 32 lists the treatment related adverse events occurring in 2 or more subjects (ofloxacin otic arm).

Table 32. Treatment related adverse events occurring in two or more subjects (ofloxacin otic arm)

Event	Total Number (%)
Earache	5 (2)
Otorrhagia	3 (1)
Tinnitus	2 (1)
Taste distortion	5 (2)
Rash	3 (1)
Fever	2 (1)
Paresthesia	2 (1)

Conclusion

The results of this study show that ofloxacin otic solution provides a safe and effective therapy for children with acute otitis media with tympanostomy tubes.

- Significantly more clinically evaluable subjects treated with ofloxacin otic solution achieved dry ear at follow-up (85%) than subjects treated in the historical practice (64%) or current-practice (71%) groups.
- Overall, ofloxacin otic solution eradicated pathogenic organisms related to acute purulent otorrhea in 96.3% of microbiologically evaluable subjects.
- Ofloxacin otic solution was generally well tolerated with most reported side effects mild to moderate in severity.

VII. Summary of Supporting Data (page 1)

Study	Study Design	N	Treatments*	Primary Findings	Microbiologic Response
PRT-02 Jones[9] OE Adults	Randomized, evaluator-blind, multicenter	314	158 FLOXIN® Otic 10 drops BID x 10 days 156 Cortisporin Otic Solution 4 drops QID x 10 days	Overall clinical response (ITT) FLOXIN Otic Cortisporin 68% 71%	Microbiologic eradication FLOXIN Otic Cortisporin 85% 88%
PRT-03 Jones[9] OE Children	Randomized, evaluator-blind, multicenter	287	143 FLOXIN Otic 5 drops BID x 10 days 144 Cortisporin Otic Solution 3 drops QID x 10 days	Overall clinical response (ITT) FLOXIN Otic Cortisporin 82% 81%	Microbiologic eradication FLOXIN Otic Cortisporin 98% 100%
PRT-016[5] OE Adolescents >12 years and Adults	Randomized, activecontrolled, evaluatorblind, multicenter	345	171 FLOXIN Otic 10 drops once daily x 7-10 days 174 Cortisporin Otic Suspension 4 drops QID x 7-10 days	Sponsor-determined overall clinical response FLOXIN Otic Cortisporin 90.6% 86.4%	Overall microbiologic eradication (by subject) FLOXIN Otic Cortisporin 98.2% 96.7%
PRT-017[5] OE Children 9 months to 12 years	Randomized, activecontrolled, evaluatorblind, multicenter	278	140 FLOXIN Otic 5 drops once daily x 7-10 days 138 Cortisporin Otic Suspension 3 drops QID x 7-10 days	Data combined for all subjects in studies 016 and 017	Data combined for all subjects in studies 016 and 017

OE: otitis externa
*10 drops = 0.50 mL
5 drops = 0.25 mL

Summary of Supporting Data (page 2)

Study	Study Design	N	Treatments*	Primary Findings	Microbiologic Response
PRT-020[6] sNDA OE Children = 6 months and Adults	Open-label, multicenter	489	FLOXIN® Otic 5 drops QD x 7 days FLOXIN Otic 10 drops QD x 7 days	Overall clinical response FLOXIN Otic 90.7%	Microbiologic eradication FLOXIN Otic 95.7%
PRT-06 Agro[7] CSOM	Multicenter, open-label, prospective with historical and concurrent practice control groups	207 prospective 185 HPC 54 CPC	FLOXIN® Otic 10 drops BID x 14 days	Clinical cure FLOXIN Otic HPC CPC 91% 67% 70%	Microbiologic eradication FLOXIN Otic 100% Most common pathogens: *S aureus, P aeruginosa, P mirabilis, E faecalis*
PRT-08 Goldblatt[4] AOM TT	Multicenter, randomized, parallel-group, evaluator-blind	474 228 FLOXIN Otic 5 drops BID x 10 days 246 Augmentin 40 mg/kg/day x 10 days		Overall clinical cure FLOXIN Otic Augmentin 76% 68%	Microbiologic eradication FLOXIN Otic Augmentin 96% 67%
PRT-07 Dohar[2] AOM TT	Multicenter, open-label, prospective with historical and concurrent practice control groups	226 prospective 218 HPC 48 CPC	FLOXIN Otic 5 drops BID x 10 days	Clinical cure FLOXIN Otic HPC CPC 85% 64% 71%	Microbiologic eradication FLOXIN Otic 96.3% Most common pathogens: *S aureus, P aeruginosa, H influenzae, S pneumoniae, M catarrhalis*

CSOM: chronic suppurative otitis media with perforated tympanic membrane
AOM TT: acute otitis media with tympanostomy tubes

VIII. Clinical and Disease Management Intervention Strategies

At this time, no clinical or disease management intervention strategies are proposed in association with the use of FLOXIN® Otic.

IX. Economic Benchmarking[1]*

There are no formal economic analyses of the impact of FLOXIN Otic for treating any otic infection. However, there are health economic analyses for both otitis externa and acute otitis media with tympanostomy tubes, and some of the results are discussed below.[39]

A. Introduction to the Disease Models for Otitis Externa and Acute Otitis Media with Tympanostomy Tubes[2]*

To gain a better understanding of costs and services used in association with otitis externa (OE) and acute otitis media with tympanostomy tubes (AOM TT), Daiichi sponsored the development of Disease Models (a unique "TRU Disease Model"[1] for each condition) that condense three years of claims data, 1999 to 2001, aggregated from more than 27 million patients into meaningful and actionable data sets.[39] In developing this information for OE, over 360,000 patients were evaluated. In developing this information for AOM TT, over 76,000 patients were evaluated.

To create these data sets, raw data from ICD-9-CM diagnosis codes found on medical claims were extracted and processed into "episodes" through a widely used and accepted episoding methodology, Episode Treatment Groups™ (ETGs™).[3*] These episoded data were then combined with specific stratifications, including demographics (e.g., region, age, gender, comorbidities) and pharmacotherapy. This combination produced homogeneous groups for collecting and reporting comparative disease-specific episode data.

1* This entire section is excerpted from Managed Care Measures, LLC (Otitis Externa Benchmarks™ 2002 & Acute Otitis Media with Tympanostomy Tubes Benchmarks™ 2002). Copyright Managed Care Measures, LLC 2003. All rights reserved. (Complete copies of these publications are supplied with this Dossier.)

2* "Disease Benchmarks™", "Disease Benchmarks for Otitis Externa™", "Disease Benchmarks for Acute Otitis Media with Tympanostomy Tubes™", "Total Resource Utilization™", "TRU™", "TRU Benchmarks™" and "TRU Disease Models™" are trademarks and/or service marks owned by Managed Care Measures, LLC. A United Sates Patent is pending for TRU Disease Models.

3* "ETG" or "ETGs" refers to "Episode Treatment Groups", episode-creating software owned by Symmetry Health Data Systems, Inc., which was used for the data presented in *Disease Benchmarks for Otitis Externa* and *Disease Benchmarks for Acute Otitis Media with Tympanostomy Tubes*. . "ETG™", "ETGs™", and "Episode Treatment Groups™" are trademarks owned by Symmetry Health Data Systems, Inc. and are used under a grant of license. Episode Treatment Groups™ (ETG™) is protected under United States Patent No. 5,835,897.US and foreign patents pending.

This process for analyzing data produces information known as Total Resource Utilization (TRU) Benchmarks™. This benchmark information is designed to better enable payers, plans, and providers to:

- Understand the total cost of care for a disease.
- Observe how disease treatment options impact resource utilization.
- Compare internal resource utilization data to external benchmarks and thereby gauge performance.

B. Key Facts about the Disease Models

- The Disease Model for an acute disease, such as OE and AOM TT, records and reports the duration and frequency of episodes present per patient, per observation year.
- "Episode duration" refers to the length of time between the first medical service that started the episode and the last medical service provided to a patient before a pre-defined "clean period" is reported, during which no further disease-specific care is received.
- Episodes are categorized by the presence of claims for specific drug classes. To be classified with the use of a drug class, at least one claim from a specific drug class (identified by NDC code) was required to be present within the episode and at any point in time during the episode.
- All episode-level data is captured starting at the beginning of each episode of care, and ending at either the end of episode (when the patient no longer receives care for the specific disease), or at the 365th day of the episode.
- Economic data (ie, costs) represents dollar amounts of charges submitted or billed by a practitioner or institution to the health plan or insurer for payment. Utilization data (ie, units of use) measure the interactions and services consumed by patients during an episode of care. This information is collected across the entire continuum of patient care including inpatient, outpatient, emergency room, and pharmacy services.

C. Key Findings – Disease Benchmarks for Otitis Externa™

- The average OE patient was 25.7 years old and had 1.8 otitis externa episodes per year, with each episode lasting on average 21 days. Episode duration was nearly 42 days for patients younger than 1 year of age. (Tables 33 and 34)

- The presence of other acute infectious comorbidities was observed in about 72% of OE episodes, the most common of which were acute upper respiratory tract infection (observed in 40.2% of episodes), acute pharyngitis (observed in 37.1% of episodes), acute sinusitis (observed in 25.2% of episodes), and acute bronchitis (observed in 19.6% of episodes). (Table 33)

- The average cost for an OE episode was $317, about $226 of which was attributable to outpatient services and $59 to prescription drugs. On average, each episode contained about 2 outpatient services and between 1 and 2 prescription drugs. The average cost per OE episode "with surgery" was $3,992 and $210 "without surgery". (Table 35)

- Overall, oral antibiotic use was observed in 58% of episodes, while otic antibiotic monotherapy - that is, episodes in which no oral antibiotics were used - was observed in only 16% of episodes. In the least complicated OE episodes (ie, those without surgery and without comorbidities), oral antibiotics were used in 49% and otic antibiotic monotherapy was observed in 24% of episodes. (Tables 36 and 37)

- Among all OE episode types, the use of otic antibiotic monotherapy was associated with the lowest total episode costs. In OE episodes without surgery, the use of oral antibiotic monotherapy was associated with total episode costs of $225; in the same population, otic antibiotic monotherapy was associated with total episode costs of $147. (Table 38)

- With respect to OE episodes without surgery (with or without comorbidities), the use of quinolone-based otic solutions was associated with lower total episode costs than the use of quinolone-based otic suspensions. (Tables 39 and 40)

- Additionally, episodes with use of quinolone-based otic suspensions reported equal, if not greater, concurrent use of additional otic corticosteroids and otic analgesics than episodes with use of quinolone-based otic solutions. (Tables 41 and 42)

- During the trend period 1999 through 2001, the use of oral antibiotics decreased slightly and there was a corresponding increase in the use of otic antibiotics - most notably when used as the only form of antibiotic pharmacotherapy. The use of aminoglycoside-based products decreased during this timeframe and the use of quinolone-based products increased. (Table 36)

D. Key Findings – Disease Benchmarks for Acute Otitis Media with Tympanostomy Tubes™

- More than 40% of all patients with AOM TT were between the ages of 2 and 3. Eighty-four percent of all patients had evidence of at least one infectious comorbidity, the most common of which were non-specific acute upper respiratory infection, acute pharyngitis, and acute sinusitis. (Table 43)

- Three types of episodes were observed in this analysis: AOM with Primary TT, which represents the first observed placement of tympanostomy tubes; AOM with Secondary TT, which represents AOM episodes with additional tympanostomy tube services; and Subsequent AOM, representing all AOM episodes following a "Primary TT" episode.

- The average cost for an AOM with Primary TT episode was nearly $3,200. Approximately 93% of these costs were generated in the outpatient environment. (Table 44)

- The average cost for an AOM with Secondary TT episode was approximately $2,800. While outpatient costs were still the primary driver, they were less than in "Primary TT" episodes; however inpatient costs in "Secondary TT" episodes were more than twice as high. (Table 44)

- The average cost for a Subsequent AOM episode was approximately $241, with $173 attributed to outpatient services and $44 attributed to pharmacy services. (Table 44)

- The average duration for an AOM with Primary TT episode was 78.6 days, 66.2 days for a "Secondary TT" episode, and 17.5 days for each Subsequent AOM episode. (Table 45)

- Evidence of oral antibiotic use was observed in 76.5% of all AOM with Primary TT episodes: 53.5% as oral monotherapy (ie, no otic antibiotics) and 23% in combination with otic antibiotics. Otic antibiotic monotherapy (ie, no oral antibiotics) was observed in only 3.2% of episodes, and the otic antibiotic agents most commonly used were quinolone-based solutions. (Table 46)

- Moving from AOM episodes with tympanostomy tubes into Subsequent AOM episodes, use of oral antibiotics decreased to 52.2% and use of otic antibiotic monotherapy increased to 5.1%. (Table 46)

- In Subsequent AOM episodes, use of otic agents as the sole form of antibiotic pharmacotherapy was generally associated with lower episode costs than episodes with the sole use of oral agents (except for those episodes with use of penicillins). Additionally, the average episode cost was similar for otic monotherapy regardless of the class used (ie, aminoglycoside or quinolone). (Tables 48 and 49)

E. Disease Model Methodology – Otitis Externa

1 Patient selection

Patients were selected for observation based on the presence of the following ETG-defined episodes of care:

- ETG 327 (Otitis with major surgery)
- ETG 328 (Otitis with minor surgery)
- ETG 329 (Otitis without surgery)
- ETG 336 (Other ENT infection, with surgery)
- ETG 337 (Other ENT infection, without surgery)

Of these episodes, only those containing diagnosis codes for otitis externa (ICD-9 codes 380.1 or 380.2) were selected for analysis.

2 Episode stratification

In addition to segmentation by patient demographics, otitis externa episodes were segmented by clinical markers including the following:

- **Episode type**. Episodes were segmented by the presence of surgical procedures indicative specific to advanced treatment of the disease. Episodes were placed into 1 of 2 mutually exclusive groups based on the following ETG definitions:
  - — Otitis externa with surgery (ETGs 327, 328, and 336)
  - — Otitis externa without surgery (ETGs 329 and 337)

- **Comorbidity prevalence**. Episodes were segmented by the presence of other acute infectious conditions, identified by diagnosis codes. A marker was established by the presence of at least one (1) medical claim with the following ICD-9 diagnosis codes present during the episode:
  - — Acute bronchitis: 466.xx

- Acute laryngitis and tracheitis: 464.xx
- Acute nasopharyngitis: 460
- Acute pharyngitis: 462
- Acute sinusitis: 461.x
- Acute tonsillitis: 463
- Chronic sinusitis: 473.x
- Other acute upper respiratory infection: 465.x

3 Pharmacotherapy segmentation

Episodes were categorized by the presence of claims for specific drug classes. To be classified with the use of a drug class, at least one claim from a specific drug class (identified by NDC drug code) was required to be present within the episode of care, at any point in time during the episode. The use of the following drug classes was observed:

- Oral antibiotics
- Otic antibiotics, including:
  - Aminoglycoside-based otic suspensions
  - Aminoglycoside-based otic solutions
  - Quinolone-based otic suspensions
  - Quinolone-based otic solutions
- Otic analgesics
- Otic corticosteroids (non-antibiotic)

F. Disease Model Methodology – Acute Otitis Media with Tympanostomy Tubes

1 Patient selection

Patients were identified by the presence of ETGs 327, 328, and 329 and the additional presence of tympanostomy placement services by CPT-4 coding (codes 69433-69436).

Once unique patients were selected, the first AOM episode with tympanostomy placement services was identified. From that point in time, and moving forward, all other AOM episodes were captured and analyzed (see the figure below). In all, there were 3 mutually exclusive and mutually exhaustive episode types observed in this analysis:

- **AOM with Primary Tympanostomy Tube Placement (TT).** These acute otitis media episodes are the first episodes reported in a patient history with tympanostomy tube placement services.

- **AOM with Secondary Tympanostomy Tube Placement (TT).** These acute otitis media episodes also contain tympanostomy tube placement services, and occur after an "AOM with Primary TT" episode.

- **Subsequent AOM**. These acute otitis media episodes also occur after an "AOM with Primary TT" episode, but do not contain any tympanostomy tube placement services.

Once an AOM episode was captured and labeled, it was placed into the study period in which it belongs (ie, 1999, 2000, or 2001).

2 Episode stratification

In addition to segmentation by patient demographics and episode type (listed above), episodes were segmented by clinical markers including the following:

- **Comorbidity prevalence**. Episodes were segmented by the presence of other acute infectious conditions, identified by diagnosis codes. A marker was established by the presence of at least one (1) medical claim with the following ICD-9 diagnosis codes present during the episode:
  - Acute bronchitis: 466.xx
  - Acute laryngitis and tracheitis: 464.xx
  - Acute nasopharyngitis: 460
  - Acute pharyngitis: 462
  - Acute sinusitis: 461.x
  - Acute tonsillitis: 463
  - Chronic sinusitis: 473.x
  - Other acute upper respiratory infection: 465.x

3 Pharmacotherapy segmentation

Episodes were categorized by the presence of claims for specific drug classes. To be classified with the use of a drug class, at least one claim from a specific drug class (identified by NDC drug code) was required to be present within the episode, at any point in time during the episode. The use of the following drug classes was observed:

- Oral antibiotics
- Otic antibiotics, including:
  - Aminoglycoside-based otic suspensions
  - Aminoglycoside-based otic solutions
  - Quinolone-based otic suspensions
  - Quinolone-based otic solutions
- Otic analgesics
- Otic corticosteroids (non-antibiotic)

G. Data Highlights – Disease Benchmarks for Otitis Externa

Table 33. Otitis Externa Three Year Demographic Trends (All Episodes)

Demographic	Year		
	1999	2000	2001
Average Age	**24.1**	**24.3**	**25.7**
Age Distribution	**Percent of Episodes**		
0-1 Years Old	3.5%	2.7%	1.8%
2-3 Years Old	9.9%	9.3%	8.2%
4-6 Years Old	10.8%	10.7%	10.2%
7-12 Years Old	20.8%	22.1%	20.9%
13-17 Years Old	8.8%	8.8%	8.8%
18-64 Years Old	41.0%	42.1%	46.0%
65+ Years Old	5.2%	4.4%	4.1%
Gender	**Percent of Episodes**		
Female	55.4%	54.4%	54.8%
Male	44.6%	45.6%	45.2%
One or More Listed Comorbidities	75.5%	74.2%	71.9%
Acute Bronchitis	20.1%	21.4%	19.6%
Acute Laryngitis and Tracheitis	5.9%	6.3%	5.7%
Acute Nasopharyngitis	5.4%	5.6%	5.2%
Acute Pharyngitis	43.7%	40.6%	37.1%
Acute Sinusitis	25.1%	25.3%	25.2%
Acute Tonsillitis	9.6%	9.6%	8.2%
Chronic Sinusitis	45.8%	42.7%	40.2%
Other Acute URI	13.1%	13.1%	12.6%

Table 34. Otitis Externa Episode Analysis (2001)

Demographic	Number of Episodes per Year	Average Episode Duration (in Days)
Overall (All Patients/Episodes)	**1.8**	**20.5**
Age Group		
0-1 Years Old	1.9	41.9
2-3 Years Old	3.6	26.4
4-6 Years Old	2.7	18.6
7-12 Years Old	1.9	14.6
13-17 Years Old	1.6	15.4
18-64 Years Old	1.4	21.7
65+ Years Old	1.5	28.6
Gender		
Female	1.7	20.4
Male	1.8	20.7
Episode Type		
Otitis Externa with Surgery	---	84.2
Otitis Externa without Surgery	---	18.7
with Comorbidities	---	19.4
without Comorbidities	---	17.0

Table 35. Otitis Externa Costs and Units by Episode Type (2001)

Service Category	Overall (All Episodes)		OE with Surgery		OE without Surgery	
	Units of Use Per Episode	Costs Per Episode	Units of Use Per Episode	Costs Per Episode	Units of Use Per Episode	Costs Per Episode
Inpatient Ancillary	0.01	$ 3.37	0.07	$ 49.41	0.01	$ 2.03
Inpatient Facility	0.00	$ 7.07	0.01	$ 77.01	0.00	$ 5.03
Inpatient Management	0.01	$ 0.73	0.03	$ 4.39	0.00	$ 0.62
Inpatient Surgical	0.00	$ 0.94	0.02	$ 31.81	0.00	$ 0.04
Inpatient Total	**0.02**	**$ 12.11**	**0.14**	**$ 162.62**	**0.01**	**$ 7.73**
Outpatient Ancillary	0.44	$ 60.29	3.97	$ 1,228.57	0.34	$ 26.32
Outpatient Management	1.52	$ 118.83	4.70	$ 922.84	1.43	$ 95.44
Outpatient Surgical	0.09	$ 46.39	2.05	$ 1,508.18	0.03	$ 3.88
Outpatient Total	**2.06**	**$ 225.51**	**10.72**	**$ 3,659.59**	**1.80**	**$ 125.65**
Emergency Room	**0.18**	**$ 21.23**	**0.31**	**$ 39.58**	**0.18**	**$ 20.69**
Pharmacy	**1.51**	**$ 58.56**	**3.06**	**$ 130.91**	**1.47**	**$ 56.45**
Total Episode Costs	**---**	**$ 317.41**	**---**	**$ 3,992.70**	**---**	**$ 210.52**

Table 36. Otitis Externa Three Year Trends of Pharmacotherapy (All Episodes)

Drug Class	Year					
	1999		2000		2001	
	Percent of Episodes with Use (Total Units per Episode)					
Any Oral Antibiotic Use	**58.8%**	**(1.6)**	**57.7%**	**(1.6)**	**57.9%**	**(1.6)**
Oral Antibiotic Use Only (No Otic Antibiotics Used)	37.0%	(1.6)	35.7%	(1.6)	35.4%	(1.5)
Any Otic Antibiotic Use	**35.9%**	**(1.1)**	**37.9%**	**(1.1)**	**38.7%**	**(1.1)**
Otic Antibiotic Use Only (No Oral Antibiotics Used)	14.1%	(1.1)	15.9%	(1.1)	16.2%	(1.1)
Aminoglycoside-based Otic Suspensions	25.9%	(1.1)	22.7%	(1.1)	20.0%	(1.1)
Aminoglycoside-based Otic Solutions	7.4%	(1.1)	7.7%	(1.1)	7.1%	(1.1)
Quinolone-based Otic Suspensions	1.7%	(1.1)	5.2%	(1.1)	7.3%	(1.1)
Quinolone-based Otic Solutions	2.5%	(1.2)	4.6%	(1.2)	6.9%	(1.1)
Otic Analgesics	3.7%	(1.1)	4.6%	(1.1)	5.3%	(1.1)
Otic Corticosteroids (Non-antibiotic)	3.2%	(1.1)	3.0%	(1.1)	2.8%	(1.1)

Table 37. Otitis Externa Pharmacotherapy by Episode Type (2001)

Drug Class	Otitis Externa Episode Type							
	With Surgery (Overall)		Without Surgery (Overall)		Without Surgery, with Comorbidities		Without Surgery, without Comorbidities	
	Percent of Episodes with Use (Total Units per Episode)							
Any Oral Antibiotic Use	**74.8%**	**3.3**	**57.4%**	**1.5**	**60.9%**	**1.5**	**48.9%**	**1.4**
Oral Antibiotic Use Only (No Otic Antibiotics Used)	42.1%	2.9	35.3%	1.5	39.7%	1.5	24.1%	1.3
Any Otic Antibiotic Use	**36.7%**	**1.5**	**38.7%**	**1.1**	**34.9%**	**1.1**	**48.3%**	**1.1**
Otic Antibiotic Use Only (No Oral Antibiotics Used)	4.1%	1.2	16.5%	1.1	13.8%	1.1	23.5%	1.1
Aminoglycoside-based Otic Suspensions	16.7%	1.3	20.1%	1.1	18.1%	1.1	25.2%	1.1
Aminoglycoside-based Otic Solutions	2.7%	1.1	7.2%	1.0	6.2%	1.0	9.8%	1.1
Quinolone-based Otic Suspensions	7.7%	1.3	7.2%	1.1	6.6%	1.1	8.9%	1.1
Quinolone-based Otic Solutions	16.6%	1.3	6.6%	1.1	6.3%	1.1	7.2%	1.1
Otic Analgesics	5.6%	1.1	5.3%	1.1	5.3%	1.1	5.3%	1.1
Otic Corticosteroids (Non-antibiotic)	1.0%	1.2	2.8%	1.1	2.4%	1.1	4.0%	1.1

Table 38. Otitis Externa Total Episode Costs by Antibiotic Use and Episode Type (2001)

Episode Type	Any Oral Antibiotic Use	Any Otic Antibiotic Use	Otic and Oral Antibiotic Use	Oral Antibiotic Use Only (No Otics)	Otic Antibiotic Use Only (No Orals)
Otitis Externa with Surgery	$4,372.37	$5,093.98	$5,307.44	$3,646.87	$3,378.95
Otitis Externa without Surgery	$259.82	$243.74	$315.54	$224.74	$147.40
with Comorbidities	$254.57	$246.94	$ 313.55	$223.14	$144.73
without Comorbidities	$276.27	$237.91	$ 319.82	$231.40	$151.35

Table 39. Otitis Externa Episode Costs by Pharmacotherapy and Episode Type - Otic Antibiotic Monotherapy (2001)

Service Category	Otitis Externa without Surgery, without Comorbidities			
	Aminoglycoside-based Otic Suspensions	Aminoglycoside-based Otic Solutions	Quinolone-based Otic Suspensions	Quinolone-based Otic Solutions
Inpatient	$0.00	$0.77	$0.00	$0.99
Outpatient	$82.14	$85.48	$95.25	$97.16
Emergency Room	$10.19	$13.03	$8.46	$4.11
Pharmacy	$32.01	$32.00	$71.67	$49.62
Total Episode Costs	**$124.34**	**$131.28**	**$175.38**	**$151.88**

Table 40. Otitis Externa Episode Costs by Pharmacotherapy and Episode Type - Otic Antibiotic Monotherapy (2001)

Service Category	Otitis Externa without Surgery, without Comorbidities			
	Aminoglycoside-based Otic Suspensions	Aminoglycoside-based Otic Solutions	Quinolone-based Otic Suspensions	Quinolone-based Otic Solutions
Inpatient	$0.74	$ 0.65	$0.00	$0.00
Outpatient	$86.06	$ 84.51	$105.27	$103.21
Emergency Room	$13.05	$ 13.19	$7.88	$7.61
Pharmacy	$32.12	$ 30.86	$73.21	$51.56
Total Episode Costs	**$131.96**	**$ 129.21**	**$186.36**	**$162.38**

Table 41. Otitis Externa Concurrent Pharmacotherapy (Otic Analgesic Use) by Otic Antibiotic Use and Episode Type (2001)

Otic Antibiotic Class	Episode Type							
	OE with Surgery (Overall)		OE w/o Surgery (Overall)		OE w/o Surgery, with Comorbidities		OE w/o Surgery, w/o Comorbidities	
	Percent of Episodes with Use (Total Units per Episode)							
Aminoglycoside-based Otic Suspensions	8.2%	1.2	4.3%	1.1	4.4%	1.1	4.1%	1.1
Aminoglycoside-based Otic Solutions	11.1%	1.5	4.9%	1.1	5.4%	1.1	4.2%	1.1
Quinolone-based Otic Suspensions	7.2%	1.2	6.2%	1.1	6.5%	1.1	5.6%	1.1
Quinolone-based Otic Solutions	9.9%	1.1	5.5%	1.1	5.5%	1.1	5.3%	1.1

Table 42. Otitis Externa Concurrent Pharmacotherapy (Otic Corticosteroid Use) by Otic Antibiotic Use and Episode Type (2001)

Otic Antibiotic Class	Episode Type							
	OE with Surgery (Overall)		OE w/o Surgery (Overall)		OE w/o Surgery, with Comorbidities		OE w/o Surgery, w/o Comorbidities	
	Percent of Episodes with Use (Total Units per Episode)							
Aminoglycoside-based Otic Suspensions	1.2%	1.1	1.8%	1.1	1.8%	1.2	1.8%	1.1
Aminoglycoside-based Otic Solutions	2.0%	1.0	1.7%	1.1	1.6%	1.1	2.0%	1.1
Quinolone-based Otic Suspensions	3.4%	1.2	2.8%	1.2	2.8%	1.2	2.9%	1.2
Quinolone-based Otic Solutions	1.0%	1.3	2.5%	1.2	2.3%	1.2	2.9%	1.1

H. Data Highlights – Disease Benchmarks for Acute Otitis Externa with Tympanostomy Tubes

Table 43. AOM with TT Three Year Demographic Trends (All Patients, All Episodes)

Demographic	Year		
	1999	2000	2001
Average Age	**8.9**	**9.2**	**9.7**
Age Distribution	**Percent of Patients**		
0-1 Years Old	17.9%	17.1%	16.1%
2-3 Years Old	40.5%	42.8%	41.3%
4-6 Years Old	16.9%	16.4%	16.8%
7-12 Years Old	10.3%	8.9%	9.5%
13-17 Years Old	1.6%	1.6%	1.8%
18-64 Years Old	10.2%	11.2%	12.6%
65+ Years Old	2.5%	2.1%	1.9%
Gender	**Percent of Patients**		
Female	42.3%	41.8%	42.2%
Male	57.7%	58.2%	57.8%
One or More Listed Comorbidities	86.6%	85.3%	84.0%
Acute Bronchitis	26.8%	28.8%	26.7%
Acute Laryngitis and Tracheitis	12.9%	13.4%	12.3%
Acute Nasopharyngitis	9.5%	10.4%	10.1%
Acute Pharyngitis	48.1%	43.5%	38.2%
Acute Sinusitis	25.5%	27.4%	26.9%
Acute Tonsillitis	14.2%	14.8%	12.1%
Chronic Sinusitis	15.2%	15.1%	15.0%
Other Acute URI	65.5%	61.5%	59.4%

Table 44. AOM with TT Costs and Units by Episode Type (2001)

Service Category	Episode Type					
	AOM with Primary TT		AOM with Secondary TT		Subsequent AOM	
	Units of Use per Episode	Costs per Episode	Units of Use per Episode	Costs per Episode	Units of Use per Episode	Costs per Episode
Inpatient	0.07	$ 55.74	0.13	$ 130.16	0.01	$ 11.86
Outpatient	10.95	$2,973.88	8.21	$2,558.05	2.10	$ 173.33
Emergency Room	0.31	$ 37.97	0.18	$ 25.66	0.11	$ 11.44
Pharmacy	3.16	$ 122.17	2.24	$ 97.98	1.07	$ 43.93
Total Episode Costs	**---**	**$3,189.76**	**---**	**$2,811.85**	**---**	**$ 240.56**

Table 45. AOM with TT Episode Analysis (2001)

Demographic	Episode Type		
	AOM with Primary TT	AOM with Secondary TT	Subsequent AOM
Overall (All Patients/Episodes)	**78.6**	**66.2**	**17.5**
0 - 1 Year Old	120.0	74.9	26.5
2 - 3 Years Old	84.2	79.5	18.5
4 - 6 Years Old	60.5	62.3	15.8
7 - 12 Years Old	54.6	55.2	14.2
13 - 17 Years Old	55.8	44.4	17.8
18 - 64 Years Old	56.6	52.7	18.1
65+ Years Old	55.8	52.8	20.5
Female	78.4	66.2	17.6
Male	78.8	66.3	17.4

Table 46. AOM with TT Pharmacotherapy by Episode Type (2001)

Drug Class	Episode Type					
	AOM with Primary TT		AOM with Secondary TT		Subsequent AOM	
	Percent of Episodes with Use (Total Units per Episode)					
Any Oral Antibiotic Use	**76.5%**	**3.6**	**67.8%**	**2.8**	**52.2%**	**1.6**
Oral Antibiotic Use Only (No Otic Antibiotics Used)	53.5%	3.6	41.2%	2.8	37.7%	1.6
Any Otic Antibiotic Use	**26.2%**	**1.4**	**31.3%**	**1.5**	**19.6%**	**1.2**
Otic Antibiotic Use Only (No Oral Antibiotics Used)	3.2%	1.4	4.8%	1.5	5.1%	1.2
Aminoglycoside-based Otic Suspensions	10.8%	1.2	13.0%	1.3	7.6%	1.1
Aminoglycoside-based Otic Solutions	1.1%	1.1	1.5%	1.2	1.0%	1.0
Quinolone-based Otic Suspensions	3.4%	1.2	6.2%	1.3	3.4%	1.1
Quinolone-based Otic Solutions	13.9%	1.3	15.6%	1.4	9.1%	1.2
Otic Analgesics	0.2%	1.1	0.4%	1.2	0.2%	1.2
Otic Corticosteroids (Non-antibiotic)	6.3%	1.1	3.5%	1.0	1.1%	1.0

Table 47. Episode Costs by Antibiotic Use and Episode Type (2001)

Service Category	Any Oral Antibiotic Use	Any Otic Antibiotic Use	Otic and Oral Antibiotic Use	Oral Antibiotic Use Only (No Otics)	Otic Antibiotic Use Only (No Orals)
Primary AOM with TT	$3,417.07	$3,536.74	$3,682.71	$3,302.96	$2,484.65
Secondary AOM with TT	$3,161.93	$3,178.03	$3,426.15	$2,991.86	$1,797.31
Subsequent AOM	$319.12	$419.18	$482.95	$255.82	$237.08

Table 48. Episode Costs by Antibiotic Pharmacotherapy - Subsequent AOM Only (2001)

Service Category	Oral Antibiotic Monotherapy (No Otic Antibiotic Use)			
	Penicillins	Penicillin Combination Products	Cephalosporins	Macrolides, Extended Spectrum
Inpatient	$4.71	$17.07	$13.21	$9.90
Outpatient	$158.61	$190.85	$212.68	$192.45
Emergency Room	$14.55	$15.90	$16.94	$18.95
Pharmacy	$40.66	$95.98	$92.88	$70.76
Total Episode Costs	**$218.53**	**$319.80**	**$335.71**	**$292.06**

Table 49. Episode Costs by Antibiotic Pharmacotherapy - Subsequent AOM Only (2001)

Service Category	Otic Antibiotic Monotherapy (No Oral Antibiotic Use)			
	Aminoglycoside-based Otic Suspensions	Aminoglycoside-based Otic Solutions	Quinolone-based Otic Suspensions	Quinolone-based Otic Solutions
Inpatient	$0.00	$0.00	$0.00	$10.53
Outpatient	$179.82	$164.64	$159.50	$163.42
Emergency Room	$7.75	$5.59	$3.34	$4.40
Pharmacy	$32.61	$32.73	$71.51	$49.74
Total Episode Costs	**$220.18**	**$202.96**	**$234.35**	**$228.09**

X. Clinical Value

The preceding sections of this dossier have presented the clinical rationale for the use of FLOXIN® Otic in the management of otitis externa (OE), chronic suppurative otitis media (CSOM) with perforated tympanic membranes, and acute otitis media with tympanostomy tubes (AOM TT). This section provides a value argument for its inclusion on a health plan's formulary.

A. Scope of otic infections

- Otitis media is the most common diagnosis made by physicians who provide care to infants and children. In the United States, the prevalence of otitis media has been increasing.
- The impact of increasing bacterial resistance on otitis media management affects not only medical treatment with antimicrobial agents but also the indications for surgical intervention.
- Otitis externa, generally a localized bacterial infection, can be quite painful, and in certain patient populations (e.g., immunocompromised, diabetic) can spread to the surrounding tissue or even become life-threatening.
- A non-intact tympanic membrane allows organisms normally found in the external auditory canal, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, to enter the middle ear space and cause infection. This complicates treatment and narrows the choice of appropriate antibiotics.
- FLOXIN Otic constitutes first-line monotherapy in three otic infections: otitis externa, acute otitis media with tympanostomy tubes and chronic suppurative otitis media.

B. Clinical evidence for FLOXIN Otic

- FLOXIN Otic once daily was equally effective to Cortisporin Otic Suspension four times daily in inducing both clinical and bacteriologic cure in subjects with OE.
- In subjects with CSOM with perforated tympanic membrane, the use of FLOXIN Otic resulted in a 91% cure rate.
- FLOXIN Otic is the only FDA approved treatment for CSOM.
- Topical FLOXIN Otic is equally effective as Augmentin in subjects with AOM TT. Subjects in whom *Pseudomonas aeruginosa* was the sole pathogen isolated were excluded from the study, as this organism is not sensitive to Augmentin.
- Within the microbiologically evaluable population, a significantly higher percentage of FLOXIN Otic-treated subjects (96.5%) had an overall microbiologic response – eradication of all baseline pathogens – than did Augmentin-treated subjects (66.7%).
- FLOXIN Otic provides excellent coverage for *Pseudomonas aeruginosa* in OE, CSOM and AOM TT.
- Emergence of bacterial resistance for topical otic antibiotics, including FLOXIN Otic, is thought to be very low, which may be due to very high concentrations at the site of the infection providing eradication.
- FLOXIN Otic pioneered the use of an ototopical antibiotic in infections with an open middle ear with its indications in CSOM and AOM TT.

C. Safety of FLOXIN® Otic

- Over 6 million prescriptions for FLOXIN Otic have been written in its 5-year history. It has been repeatedly shown to be safe and generally well-tolerated.
- FLOXIN Otic has a much lower incidence of diarrhea (< 1%) compared to Augmentin (27%) in children with AOM TT.
- The most common reported adverse reactions in three clinical trials (n = 799) in OE subjects treated once daily with FLOXIN Otic were application site reaction (0.6% - 16.8%), pruritis (1% - 1.2%), earache (0.6% - 0.8%), dizziness (0.0% - 0.6%) and headache (0.2% - 0.3%). In two of these clinical studies (n = 310), the higher application site reaction rate resulted from the specific questioning of subjects.
- The most common reported adverse reactions in clinical trials in acute otitis media patients with tympanostomy tubes and chronic suppurative otitis media patients treated twice daily with FLOXIN Otic (n = 656) were taste perversion (7%), earache (1%), pruritis (1%), paraesthesia (1%), rash (1%), and dizziness (1%).
- FLOXIN Otic is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.
- FLOXIN Otic is safe to use for otitis externa even when the integrity of the tympanic membrane is in doubt. Clinical trial results showed no evidence of hearing loss based on a study with 30 pediatric subjects with AOM TT.

XI. References

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